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A STUDY OF THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) UPON THE EXPERIMENTAL CARDIOVASCULAR LESIONS PRODUCED BY ANAPHYLACTIC HYPERSENSITIVITY

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Received for publication January 9, 1950

Some months ago Hench and his co-workers (1) (2) announced their important discovery that the adrenal cortical hormone, compound E, exerts a remarkable therapeutic effect upon rheumatoid arthritis and encouraging effects upon acute rheumatic fever, and that the same beneficial effect upon rheumatoid arthritis could be obtained by stimulating adrenal cortical secretion with the adrenocorticotropic hormone of the pituitary (ACTH). The mode of action of the adrenal hormone in producing the astonishing observed therapeutic effect is completely obscure, and a new field for investigation has been opened up which, when adequately cultivated, cannot fail to yield highly important basic knowledge regarding the economy of the body and the pathogenesis of a variety of poorly understood pathological processes.

Rheumatoid arthritis and rheumatic fever are representatives of the coliagen-vascular group of diseases, so called because they are characterized especially by focal damage to collagen and to the cardiovascular system. Periarteritis nodosa, disseminated lupus erythematosus and at least some instances of clinical dermatomyositis also belong to this group. It has been shown in this laboratory that, both in the human being (3) and in the experimental animal (4), one of the members of this group, periarteritis nodosa, can result from anaphylactic hypersensitivity, and that anaphylactic hypersensitivity can produce cardiovascular lesions similar to those of rheumatic fever (5). These studies have been confirmed by many other investigators. Furthermore, one of us (6) has pointed out that rheumatoid arthritis, rheumatic fever, periarteritis nodosa and disseminated lupus erythematosus exhibit, in addition to collagen and vascular damage, many clinical and pathological features in common with the protracted type

of anaphylactic reaction represented by serum sickness and drug hypersensitivity. These various observations have suggested that anaphylactic hypersensitivity may be an important factor in the pathogenesis of the collagen-vascular diseases. The discovery of the dramatic effect of the adrenal cortical hormone upon two of the diseases of this group made it at once desirable to learn whether the hormone will affect the development of the lesions of the one member of the group now definitely known to be producible by anaphylactic hypersensitivity, namely, periarteritis nodosa, and if so, to study the mechanism of action of the hormone in that direction. To this end the experiments here reported were carried out.

EXPERIMENTAL PROCEDURE

Each of 40 albino male rabbits, averaging about 2300 grams in weight (Table III), was given intravenously a single injection of 10 cc of sterile horse serum (without preservative)[1], per kilogram of body weight. This was the sensitizing procedure used by Rich and Gregory in their studies on the experimental production of periarteritis nodosa and rheumatic-like cardiovascular lesions (4) (5). Skin tests performed twelve days later showed that all animals had developed hypersensitivity (Table I). Throughout the experiment the animals were kept in separate, adjoining cages, and were given an unrestricted amount of Rider's Complete Rabbit Pellets and water, with a weekly supplement of carrots. They were weighed every other day.

On the same day that the intravenous injection of horse serum was given, intramuscular injections of ACTH were begun. Twenty of the rabbits were given ACTH, and twenty were left untreated as controls. The ACTH was kindly supplied by Dr. Irwin C. Winter, of G. D. Searle and Co. This preparation, designated X1-134, was made from hog pituitary, and the bioassay showed that it required six gamma to produce a 25% fall in the adrenal ascorbic acid of 26 hour hypophysectomized adult rats. It contained a residual oxytocic activity of 0.05 USP units per milligram. It was received in powder form. Each day only enough required for the succeeding 24 hours was weighed, placed in a sterile flask and dissolved in sterile normal saline at a concentration of 5 mg. per cc. The solution so prepared was heated for 20 minutes in a boiling water bath for the purpose of sterilization. It is known that ACTH is stable in acid or neutral solution at 100°C. The slight precipitate which formed on heating this particular preparation was therefore probably due to some impurity. Between injections, both the solution and the dry powder were kept at 4°C in tightly stoppered containers.

Since the quantitative response of the rabbit to ACTH is not definitely known,

[1] We are indebted to Sharpe and Dohme, Inc. for generously supplying the horse serum.

TABLE I

Local reactions 24 hours after intracutaneous injection of 0.1 cc. horse serum on twelfth day after intravenous sensitizing injection

RABBIT	ACTH TREATED	RABBIT	CONTROLS
1	4.5 x 3.5 pale edema 1 cm. pink center	21	5 x 4.5 pink edema
2	4 x 3 pale edema 1 cm. pink center	22	6.5 x 5 cm. pink edema
3	2.5 x 2 cm. pink edema	23	4 x 3.5 pale edema 1 cm. pink center
4	2 x 2 cm. pink edema	24	4 x 3 cm. pale edema
5	4 x 5 cm. pale edema 1 cm. pink center	25	4 x 3.5 cm. pink edema 1.5 cm. red center
6	4.5 x 4.5 cm. pale edema 1 cm. deep pink center	26	4 x 3 cm. pink edema
7	5 x 5.2 cm. pale edema 1 cm. pink center	27	2.5 x 2 pink edema
8	5 x 4 cm. pale edema	28	6.5 x 4 cm. pink edema 1 cm. red center
9	5.5 x 3.5 cm. pale edema 1 cm. pink center	29	2.2 cm. purple center[1]
10	5.5 x 4.5 cm. pale edema	30	4 x 3.5 cm. pink edema 1 cm. purple center
11	2.5 x 2 cm. pale pink edema	31	7 x 4.5 pink edema
12	6 x 4 cm. pink edema	32	4 x 3.5 pale edema 1 cm. red center
13	3 x 3 cm. pale edema 1 cm. red center	33	4.5 x 4.5 cm. deep pink edema 1 cm. red center
14	4.5 x 3 cm. pink edema	34	2 x 2.5 pink edema
15	4 x 4 cm. pink edema	35	2 x 2.5 cm. pale edema

TABLE I—*Concluded*

RABBIT	ACTH TREATED	RABBIT	CONTROLS
16	4 x 4.5 deep pink edema	36	5 x 4.5 cm. pale edema 1 cm. red center
17	4 x 4 cm. pink edema 1 cm. red center	37	6 x 5 deep pink edema,
18	2 x 2 cm. pale edema 1 cm. purple center	38	4.5 x 3.5 pink edema 1 cm. red center
19	5 x 3.5 pink edema 1 cm. red center	39	5 x 5 cm. pink edema small red center
20	3 x 2 cm. pale edema 1 cm. red center	40	3 x 4.5 cm. pale edema 1 cm. purple center
Average:	3.8 x 3.5 cm. edema 9 pink edema 11 pale edema 6 pink center 4 red center 1 purple center		4.3 x 3.8 cm. edema 12 pink edema 7 pale edema 1 pink center 7 red center 3 purple center

[1] Limits of zone of edema not measurable because of normal thickness of skin site.

an initial dosage per kilogram of body weight about five times that given to produce therapeutic effects in man was used. The treated animals received 5 mg. of ACTH every six hours throughout the day and night during the first week. Then, because of a considerable loss of weight in several of the animals, the dosage for those animals was reduced from 20 mg. in 24 hours to 5 mg., and for the remainder the dosage was reduced to 10 mg. The weight loss appeared to be due, in part at least, to the development of anorexia toward the Rabbit Pellets, though the affected animals ate carrots eagerly. On the thirteenth day the dosage of ACTH was increased to 10 mg. per 24 hours for the animals which had exhibited the greatest weight loss, and to 20 mg. for the remainder of the treated animals. This dosage was maintained until the animals were killed by etherization (see Table III). In this first experiment the control animals were purposely given no injections of a control fluid, for we wished to avoid any possible stimulation of the adrenals by non-specific stress stimuli.

On the twelfth day of the experiment all animals were tested for hypersensitivity by the intradermal injection of 0.1 cc of the horse serum used for sensitization. On the day of death serum for precipitin tests was obtained by heart puncture. Careful autopsies were performed on all animals. There was no evidence of infection at any of the sites of injection. Sections for the microscopic study listed in Table III were made from the heart, lung, liver, spleen, both adrenals, both kid-

TABLE II

Weights of Adrenal and Thymus at Autopsy with Ratios of Each to Body Weight

ACTH TREATED					CONTROLS				
Rabbit	Adrenal mgm	Adrenal / Body × 1000	Thymus gms	Thymus / Body × 1000	Rabbit	Adrenal	Adrenal / Body × 1000	Thymus gms	Thymus / Body × 1000
	mgm		*gms*			*mgm*		*gms*	
1	332	0.13	—	—	21	207	0.08	3.6	1.35
2	320	0.12	0.8	0.29	22	175	0.07	3.2	1.36
3	252	0.14	0.6	0.33	23	205	0.07	6.9	2.53
4	312	0.13	0.8	0.32	24	157	0.06	4.0	1.6
5	388	0.16	1.0	0.30	25	252	0.11	3.1	1.24
6	380	0.15	5.6	2.13	26	262	0.10	2.0	0.76
7	295	0.11	2.5	0.96	27	172	0.08	3.8	1.73
8	275	0.11	0.8	0.31	28	190	0.08	3.5	1.45
9	320	0.12	4.4	1.65	29	165	0.05	3.5	1.08
10	205	0.08	2.4	0.96	30	170	0.06	5.1	1.75
11	300	0.12	0.9	0.37	31	205	0.07	3.9	1.45
12	235	0.12	0.6	0.29	32	205	0.08	4.2	1.7
13	340	0.14	1.3	0.52	33	175	0.05	2.3	0.69
14	405	0.13	3.1	1.00	34	100	0.04	4.4	1.74
15	242	0.08	3.5	1.18	35	170	0.07	4.2	1.68
16	270	0.11	0.3	0.12	36	170	0.06	5.1	1.85
17	180	0.07	2.1	0.83	37	205	0.09	3.9	1.64
18	185	0.08	1.6	0.65	38	235	0.08	4.7	1.62
19	150	0.07	0.4	0.19	39	225	0.10	6.5	2.83
20	245	0.10	1.7	0.69	40	185	0.07	3.4	1.31
Average	281.5	0.11	1.7	0.68	Average	191.5	0.07	4.06	1.57

neys, pancreas, thymus, testis and skeletal muscle of each animal. Other tissues were preserved for additional study. An equal number of sections of the organs of the control and treated animals were prepared and thoroughly searched for lesions. The sections of corresponding organs were of approximately the same size in both groups.

RESULTS

Table I shows that all treated and control animals developed hypersensitivity to the horse serum, as revealed by positive skin tests. The average diameter of the reactions in the control group was slightly, but hardly significantly, larger than in the treated group, though in twice as many of the controls the reactions were of the higher degrees of intensity characterized by a deep red or purple central zone.

The presence of the many pseudoeosinophils in normal rabbit's blood rendered fruitless the attempt to study accurately the response

TABLE III

ACTH Treated

RABBIT	GMS. BODY WEIGHT† AND MGM ACTH PER DAY			DAY KILLED	PRECIPITIN TITRE	FRANK PERIARTERITIS NODOSA	WELL MARKED ENDOCARDITIS	SLIGHT SUBENDOTHELIAL INFILTRATION
	1-7 Day	7-13 Day	13-Death					
1	2300 20	2400 10	2500 20	15	1:2000	+	0	0
2	2575 20	2650 10	2800 20	15	1:500	0	0	+
3	1925 20	1950* 5	1825 10	15	1:2000	0	0	0
4	2200 20	2400 10	2400 20	15	1:4000	0	0	0
5	2400 20	2375 10	2525 20	15	1:2000	0	0	0
6	2325 20	2450 10	2675 20	16	1:4000	+	+	+
7	2025 20	2200 10	2600 20	16	1:2000	+	0	+
8	2500 20	2450 10	2575 20	16	1:1000	0	0	0
9	2425 20	2475 10	2625 20	16	1:2000	0	0	0
10	2075 20	2400 10	2500 20	16	—	0	0	0
11	2475 20	2125 5	2425 10	17	1:500	0	0	+
12	2300 20	1800 5	2050 10	17	—	0	0	0
13	2200 20	2175 10	2500 20	17	—	0	0	0
14	2750 20	2900 10	3100 20	17	—	+	+	0
15	2500 20	2650 10	2950 20	17	—	0	0	0
16	2750 20	2375 5	2425 10	17	—	0	0	0
17	2050 20	2250 10	2525 20	17	—	0	0	0
18	2475 20	2425 10	2450 20	18	1:8000	0	0	0
19	2075 20	1825 5	2125 10	18	1:4000	0	0	0
20	2475 20	2450 10	2450 20	18	—	+	0	+
Average wgt.	2342	2336	2501		Total	5(25%)	2(10%)	5(25%)

† Weight on 1st day, 7th day and day of death.
* Animal ill.

TABLE III—(*Continued*)

Controls

RABBIT	GMS. BODY WEIGHT			DAY KILLED	PRECIPITIN TITRE	FRANK PERIARTERITIS NODOSA	WELL MARKED ENDOCARDITIS	SLIGHT SUBENDOTHELIAL INFILTRATION
	1-7 Day	7-13 Day	13-Death					
21	2325	2650	2675	15	1:4000	+	0	+
22	2200	2325	2350	15	1:1000	+	0	+
23	2450	2400	2725	15	1:2000	+	0	+
24	2125	2175	2500	15	1:2000	+	0	+
25	2475	2575	2500	15	1:4000	+	0	+
26	2450	2575	2625	16	1:4000	+	0	+
27	1975	2175	2200	16	1:2000	+	+	+
28	2250	2450	2450	16	1:2000	0	+	+
29	2900	3225	3200	16	1:4000	0	+	+
30	2500	2800	2900	16	1:4000	+	+	+
31	2500	2575	2725	17	1:8000	0	0	0
32	2200	2350	2475	17	—	0	+	+
33	2950	3100	3250	17	—	+	+	+
34	2125	2500	2525	17	—	+	0	+
35	2075	2300	2500	17	—	0	0	+
36	2200	2525	2750	17	—	+	+	0
37	2150	2300	2375	17	1:16000	+	+	+
38	2400	2775	2875	18	—	+	0	+
39	1875	2175	2300	18	—	0	+	+
40	2300	2625	2560	18	—	+	+	+
Average wgt.	2321	2528	2623		Total	14 (70%)	10 (50%)	18 (90%)

of the eosinophils to the injections of ACTH. However, the activity of the hormone was indicated by the enlargement of the adrenals in the treated group. At autopsy the adrenals were carefully dissected free from the surrounding tissues and weighed. As can be seen in Table II, the average weights of the glands in the treated group was 47% greater than that in the control group. It may also be noted that the average weight of the thymus in the treated group was markedly less than in the control group.

Since the purpose of this study was to learn whether the development of the cardiovascular lesions that result from protracted hypersensitivity reactions can be inhibited by the increased adrenal cortical activity stimulated by ACTH, the histological sections of heart, lung, liver, spleen, kidneys, adrenals, pancreas, testis, thymus and striated muscle of each animal were carefully examined for the presence of such lesions. The lesions found were altogether of the same character as those amply illustrated in previous reports (4) (5), and need not be re-described here. The results of the tissue study are listed in Table III.

DISCUSSION

It can be seen in Table III that 18 (90%) of the 20 animals in the control group developed well-marked vascular or cardiac lesions or both, whereas such lesions were found in only 5 (25%) of the 20 animals treated with ACTH. In addition to these lesions, 18 animals in the control group showed, each, an occasional minute lesion consisting of a slight subendothelial infiltration of mononuclear cells in the intima of arteries or in the endocardium, whereas similar minute foci were found in only 5 of the treated animals. While it would appear, therefore, that the ACTH exerted a decidedly suppressive influence upon the development of the lesions, that interpretation must be regarded as only tentative in view of the well-known and unpredictable differences in individual susceptibility to the development of periarteritis nodosa and other types of hypersensitive reactions in the sensitized human being and experimental animal (6). Further experiments are imperative, and will be carried out by ourselves and, doubtless, by others. Meanwhile, the results of this series of 40 animals are reported for the reason that, in view of the present restricted supply

of ACTH and compound E, it is desirable to have all studies comprising a reasonable number of observations placed on record.

Table I shows little, if any, difference between the intensity of the skin reactions in the treated animals and the controls. It is clear from this that the ACTH neither prevented the development of hypersensitivity nor abolished the capacity of the sensitized body to react to the antigen. It may be noted, however, that the amount of antigen delivered to each skin-test site in this pilot experiment was large (0.1 cc of undiluted antigen). It will be necessary to perform graded skin tests in order to determine whether ACTH decreases the local reactivity to the antigen. Furthermore, it should be re-emphasized that the individual tendency to develop cardiovascular lesions of hypersensitivity is not paralleled by the degree of reactivity of the skin to a test injection of antigen (4). This is comparable with the lack of parallelism between the degree of cutaneous reactivity to a given antigen and the individual tendency to develop asthma or other hypersensitivity phenomena on contact with the antigen. It is of especial interest, in relation to the present problem, that Harvey and his coworkers (8) have recently reported that ACTH exerts a strikingly beneficial therapeutic effect in patients with asthma and drug hypersensitivity.

The serum of 12 ACTH treated animals and of 12 control animals was examined for precipitins to horse serum (antigen dilution; ring test). The serum was withdrawn on the day the animals were killed. Precipitins were present in all of the sera. While the treated animals tended to have a lower titer than the controls, the difference is not marked, nor was there any correlation between the titre and the presence of the lesions (Table III).

In view of our recent observation that the overactive cells of the reticular zone of the adrenal cortex in cases of adrenogenital syndrome are characterized by the presence of basophilic cytoplasmic bodies containing ribonucleic acid (7), it is of interest that no such bodies were found in the cortical cells of the adrenals stimulated by ACTH in the present study.

SUMMARY

Forty rabbits were sensitized with horse serum in the manner known to favor the development of periarteritis nodosa and cardiac inflam-

matory lesions. Half were treated with pituitary adrenocorticotropic hormone (ACTH), the remainder serving as controls. Well-marked vascular or cardiac lesions or both were found in 18 of the 20 untreated controls, whereas such lesions were found in only 5 of the 20 animals treated with ACTH.

While these results strongly suggest that ACTH exerts an inhibitory effect upon the development of the cardiovascular lesions of hypersensitivity, further studies are required before such a conclusion can be regarded as established.

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ELECTROCARDIOGRAPHIC OBSERVATIONS DURING CARDIAC CATHETERIZATION[1]

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INTRODUCTION

Cardiac catheterization is now widely used as an aid in the diagnosis of congenital heart disease and in the study of cardio-respiratory physiology. Although the overall mortality of this procedure reported from various laboratories is low (0.1%) (2), nevertheless, there are certain complications which may arise during this procedure. These consist primarily of cardiac arrhythmias, the recognition of which is important. Several papers (1, 5, 7, 10, 11, 12, 13, 15, 16) and one book (17) have been published on potentials within the cavities of the right side of the heart. Though these authors report various types of arrhythmias incidental to their intracavitary studies, the occurrance of these arrhythmias was infrequent. There has been no report of continuous electrocardiographic studies made throughout the entire procedure of cardiac catheterization. Consequently, it was felt that such a study might aid in the reduction of complications due to cardiac arrhythmias secondary to the passage of the catheter through the various chambers and great vessels of the heart.

PROCEDURE

A total of fifty patients was studied in this series. Thirty six of these had congenital heart disease. Coronary blood flow studies (3) were performed on six patients, four of whom had hypertensive cardio-vascular disease, one syphilitic heart disease and one myocarditis

[1] Supported by grants from the Commonwealth Fund and the Carolyn Rose Strauss Foundation, given to the Department of Surgery.

* Fellow in Medicine.

† Yedz Grotto Fellow in Pediatrics.

‡ Research Fellow, U. S. Public Health Service.

TABLE 1

NO.	PATIENT	AGE	SEX	DIAGNOSIS	AURICULAR			SUPRA-VENTRIC. TACHY.		NODAL PREMATURE SYSTOLES				VENTRICULAR EXTRA-SYSTOLES		VENTRICULAR			A-V BLOCK			BUNDLE BRANCH BLOCK	
					Prem. Syst.	Flut.	Fibr.	Aur.	Nod.	C	U	M	L	Single	Multi.	Tach.	Flut.	Fibr.	1st	2nd	3rd	Rt.	Lt.
1.	G. K.	10	M	Rhabdomyoma of the left ventricle and septum. (Autopsy)											X	X		X					
2.	B. S.	9	M	Pulmonic stenosis with a patent foramen ovale.						X	X	X			X	X							
3.	R. R.	36	F	Functional truncus arteriosus. (Autopsy)	X								X		X	X							
4.	S. E.	21	M	Pulmonic stenosis with an atrial septal defect.								X											
5.	E. G.	44	F	Hypertensive heart disease.							X	X			X	X							
6.	N. S.	51	F	Hypertensive heart disease.											X	X						X	
7.	W. B.	.5	M	Auricular septal defect.				X	X		X	X											
8.	J. C.	36	F	Mitral stenosis.																			
9.	D. S.	7	F	Tetralogy of Fallot.	X			X		X	X	X			X	X			X	X	X		
10.	R. S.	7	M	Patent ductus arteriosus.	X			X				X			X	X							
11.	M. C.	32	F	Pulmonic stenosis with a patent foramen ovale.								X			X	X			X				
12.	R. S.	.6	M	Tetralogy of Fallot.						X	X	X			X	X							
13.	K. F.	4	F	Pulmonary veins emptied into right auricle. (Autopsy)							X	X											
14.	J. Z.	44	M	Hypertensive heart disease.							X	X			X	X							
15.	R. H.	35	M	Patent ductus arteriosus. (Autopsy)	X							X			X	X							

16.	R. H.	7	M	Left superior vena cava, pulmonary hypertension and patent foramen ovale.	X						X	X													
17.	G. B.	20	M	Idiopathic dilatation of the pulmonary artery.							X				X										
18.	H. H.	23	M	Patent ductus arteriosus.								X			X	X									
19.	J. G.	2	M	Pulmonary veins entered superior vena cava. (Autopsy)	X				X		X	X			X	X									
20.	M. E.	60	F	Hypertensive heart disease.							X				X										
21.	R. S.	7	M	Patent ductus arteriosus.	X				X	X	X	X			X	X	X								
22.	R. B.	32	M	Cor pulmonale.	X										X										
23.	A. F.	9	F	Auricular septal defect.	X							X		X											
24.	C. L.	7	M	Ventricular septal defect.	X							X			X	X									
25.	E. A.	11	M	Pulmonic stenosis with a patent foramen ovale.	X							X													X
26.	E. P.	46	M	Patent ductus arteriosus, mitral stenosis and auricular fibrillation.											X	X	X								
27.	A. Y.	8	F	Eisenmenger's Complex.	X			X	X			X			X	X									X
28.	C. S.	7	F	Pulmonary arteriovenous aneurism.	X							X			X	X									
29.	S. A.	47	M	Luetic aortic regurgitation.	X										X	X									
30.	J. T.	9	F	Pulmonic stenosis with a patent foramen ovale.	X				X			X			X	X									
31.	H. S.	19	M	Tetralogy of Fallot.											X	X									
32.	H. M.	28	F	Pulmonary arteriovenous aneurism.	X							X			X	X									
33.	P. M.	4	F	Transposition of the aorta with overriding of the pulmonary artery.	X					X					X	X									
34.	E. W.	34	F	Patent ductus arteriosus.	X				X	X	X	X			X	X									
35.	P. C.	4	F	Pulmonary hypertension.		X					X				X	X				X					X
36.	M. G.	37	F	Ruptured aortic valve cusps. (Autopsy)	X							X	X		X										

TABLE 1—*Concluded*

NO.	PATIENT	AGE	SEX	DIAGNOSIS	AURICULAR			SUPRA-VENTRIC. TACHY.		NODAL PREMATURE SYSTOLES				VENTRICULAR EXTRA-SYSTOLES		VENTRICULAR			A-V BLOCK			BUNDLE BRANCH BLOCK	
					Prem. Syst.	Flut.	Fibr.	Aur.	Nod.	C	U	M	L	Single	Multi.	Tach.	Flut.	Fibr.	1st	2nd	3rd	Rt.	Lt.
37.	M. R.	32	M	Myocarditis.											X	X							
38.	A. G.	19	M	Eisenmenger's Complex.	X			X			X				X	X							
39.	L. E.	9	M	Auricular defect. Nodal rhythm prior to catheterization.	X			X			X	X	X		X	X							
40.	M. R.	1	F	Transposition of the great vessels.	X							X			X	X							
41.	A. T.	3	F	Tetralogy of Fallot.											X	X					X		
42.	L. H.	5	F	Transposition of the great vessels.		X									X	X							
43.	G. C.	4	M	Ventricular septal defect.	X	X			X			X			X	X							
44.	C. G.	9	F	Transposition of the great vessels.	X				X	X					X	X							
45.	M. M.	19	F	Auricular septal defect.	X				X	X		X			X	X							
46.	D. N.	6	F	Pulmonic stenosis with a patent foramen ovale. Nodal rhythm present prior to catheterization.	X					X		X			X	X						X	
47.	A. G.	11	M	Patent ductus arteriosus.	X					X	X	X			X	X						X	
48.	A. L.	36	F	Auricular septal defect.	X			X							X	X	X						
49.	L. S.	2	F	Patent ductus arteriosus.	X							X			X	X							
50.	N. H.	7	F	Transposition of the aorta with overriding of the pulmonary artery.	X					X	X	X	X		X	X							
				Total	30	3	0	7	9	11	18	32	4	1	43	39	6	1	3	1	2	6	0
				Percentage of total cases	60%	6%	0%	14%	18%	22%	36%	64%	8%	2%	86%	78%	12%	2%	6%	2%	4%	12%	0%

of unknown etiology. Of the remaining cases, one had rheumatic heart disease with mitral stenosis and was studied in preparation for cardiac surgery. In another case, idiopathic dilatation of the pulmonary artery was present, and two patients had cor pulmonale. Autopsy diagnoses of myocardial rhabdomyoma were made in one case and ruptured aortic valve cusp in another. Two cases with pulmonary arteriovenous aneurisms were also studied. The youngest patient in this series was six months old and the oldest fifty one years old. Children under eight years of age, studied in this series were premedicated with morphine and scopolamine. One of us, (I. R. G.) was present at the controls of a direct writing electrocardiograph throughout the catheterization of the fifty patients in this series.

Prior to the beginning of the catheterization, the three standard limb leads were recorded as controls. The fluoroscopic table, the electrocardiograph, the patient and the operator manipulating the catheter were grounded to reduce electrical interference. A continuous electrocardiographic record was then recorded throughout the procedure. When possible, lead 1 was used so that the origin of ventricular premature systoles could be determined. However, in numerous instances this was impossible due to electrical interference caused by the manipulation of the catheter in the antecubital vein. Consequently, when such interference arose, and the left arm was being used, the electrocardiographic tracing was taken using Lead 2; and when the catheter was being passed through the right antecubital vein, Lead 3 was used. Following the completion of the procedure, each electrocardiographic tracing was carefully analyzed. Table 1 summarizes the results.

RESULTS AND DISCUSSION

Variations in the heart rate and tachycardias of sinus mechanism were not considered of importance in this study. Sinus arrhythmia is common in children, and the majority of the patients in this study had a sinus tachycardia prior to cardiac catheterization. In the younger patients, scopolamine premedication may have been a factor in causing sinus tachycardia (6). Consequently, our observations will deal only with abnormal mechanisms occurring below the sino-auricular node. Only one patient (#8) of the fifty studied in this series did not develop any changes in rhythm during cardiac catheterization.

Using the criteria of Katz (9), the disturbances of cardiac rhythm encountered in this study are classified as follows:

I. Supraventricular Mechanisms
  A. Premature Systoles
    1. Auricular
    2. Nodal
      a. Coronary
      b. Upper
      c. Middle
      d. Lower
  B. Tachycardia.
    1. Auricular
    2. Nodal
  C. Auricular Flutter
  D. Auricular Fibrillation

II. Ventricular Mechanisms
  A. Premature Systoles
  B. Tachycardia
  C. Flutter
  D. Fibrillation

III. Conduction Disturbances
  A. Auriculoventricular Block
    1. First degree
    2. Second degree
    3. Third degree
  B. Bundle Branch Block
    1. Right
    2. Left

I. SUPRAVENTRICULAR MECHANISMS

Premature Systoles:

Thirty patients (60%) of this series exhibited auricular premature systoles. These were first observed when the tip of the catheter entered the right auricle. They were most frequently seen when the catheter tip appeared to be in contact with the auricular septum, and particularly when the catheter was passing through an auricular septal defect. However, auricular premature systoles were also observed while the

catheter tip was in the right ventricle. A portion of the catheter in the right auricle coming in contact with the endocardium may explain this phenomenon. A premature auricular systole was never seen when the catheter tip was in the pulmonary artery or aorta. Hecht (7) and Kert and Hoobler (10) described an auricular premature contraction in one of their cases while the catheter was in the right auricle. Battro and Biddogia (1) observed an auricular premature systole in only one of twenty-three cases during intracavitary studies. Levine et al. (12) report auricular premature contractions in four of twenty cases while studying intracavitary potentials. In three of these cases, the catheter tip was in the right auricle, and in one it was in the right ventricle. In the last case, multiple auricular premature contractions were seen. Two or more consecutive auricular premature systoles were commonly seen in this series during cardiac catheterization.

Seventy-eight percent of the patients in this series developed nodal premature systoles. Twenty-eight percent of these were of the coronary type and were seen when the catheter tip was probing in the region of the coronary sinus. Forty-six percent of the nodal premature systoles were of the upper nodal type and were usually observed while the catheter was being advanced toward the tricuspid valve, although they occasionally appeared with the catheter in the right ventricle. The largest percentage of nodal premature systoles was of the middle type (82%) with the P wave buried in the QRS complex. These were most frequently seen as the catheter passed through the tricuspid valve. They were also numerous while the catheter was in the right ventricle. A few scattered lower nodal premature systoles were observed in four patients, but no definite correlation could be made between the location of the catheter tip and their occurrance. Once the catheter had been passed through the pulmonary or aortic valve, nodal premature systoles did not occur. No apparent relationship existed between the occurrence of nodal premature systoles and the type of heart disease or the age of the patient.

Auricular Tachycardia:

Auricular tachycardia occurred in fourteen percent of the patients in this series, all of whom had congenital heart disease. In three of these patients (#7, 39, 48) an auricular septal defect was present.

Two patients had Eisenmenger's Complex (#27, 38). One patient had a Tetralogy of Fallot (#9) and one a patent ductus arteriosus (#10). It is interesting to note that the only two cases of Eisenmenger's Complex in this series developed auricular tachycardia. Figure 1 illustrates a short burst of auricular tachycardia which occurred with the catheter in the right auricle. However, this arrhythmia was also seen to occur with the catheter tip in the right ventricle. Johnson et al. (8) have described paroxysmal auricular tachycardia occurring in one of their patients when the catheter passed through an auricular septal defect. This arrhythmia continued for two hours and ended spontaneously. Cournand et al. (4) have reported two cases of auricular tachycardia. One disappeared spontaneously and the second case ceased immediately upon the withdrawal of the catheter.

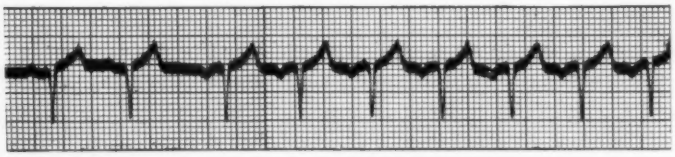

FIG. 1. This illustrates the onset of auricular tachycardia while the catheter was in the right auricle. The third complex is the beginning of the tachycardia.

Since auricular tachycardia encountered in this series was of short duration and the patients were asymptomatic, it did not interfere with the progress of the catheterization. The youngest patient exhibiting auricular tachycardia (#7) was six months old and had an auricular septal defect. The oldest patient (#48) also had an auricular septal defect and was thirty-six years old.

Nodal tachycardia was more common than auricular tachycardia and was seen in eighteen percent of this series. All of these patients had congenital heart disease, the youngest being six months and the oldest thirty-four years old. This arrhythmia occurred with the catheter in either the right auricle or ventricle and did not interfere with the progress of the catheterization. However, since the completion of this series, a persistent nodal tachycardia developed in one patient necessitating interruption of the procedure because of dyspnea

and substernal distress. This arrhythmia reverted to a normal sinus rhythm several minutes after the withdrawal of the catheter. The nodal tachycardia encountered in Case 8 is seen in Figure 2.

Auricular Flutter:

Auricular flutter developed in three patients (6%) of this series. Pulmonary hypertension was present in case #35, transposition of

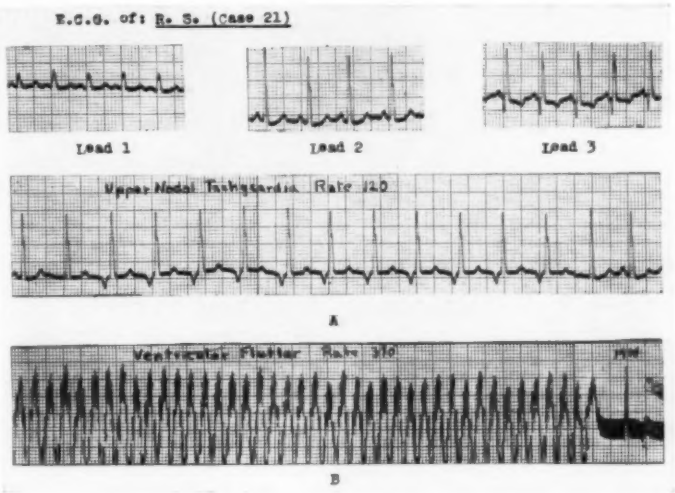

FIG. 2 (R. S. Case 21). "A" shows the three standard leads prior to catheterization. "B" illustrates the onset of nodal tachycardia at a rate of 120 per minute which occurred while the catheter was in the right auricle. In "C" ventricular flutter at a rate of 370 per minute occurred when the catheter entered the right ventricle. Upon withdrawal of the catheter into the right auricle, a precatheterization electrocardiographic pattern reappeared.

the great vessels in case #42 and a ventricular septal defect in case #43. Two were four years old (#35, 43) and one was five years old (#42). Case #42 and #43 had antecendent auricular premature systoles during the catheterization. Figure 3 illustrates aruicular flutter encountered in case #42. This developed while the catheter was in the right ventricle. In case #43, auricular flutter also appeared when the catheter was in the right ventricle. However, in case #35, this ar-

rhythmia developed while the catheter tip was in the right auricle. Auricular flutter did not give rise to any symptoms which caused interruption of the procedure.

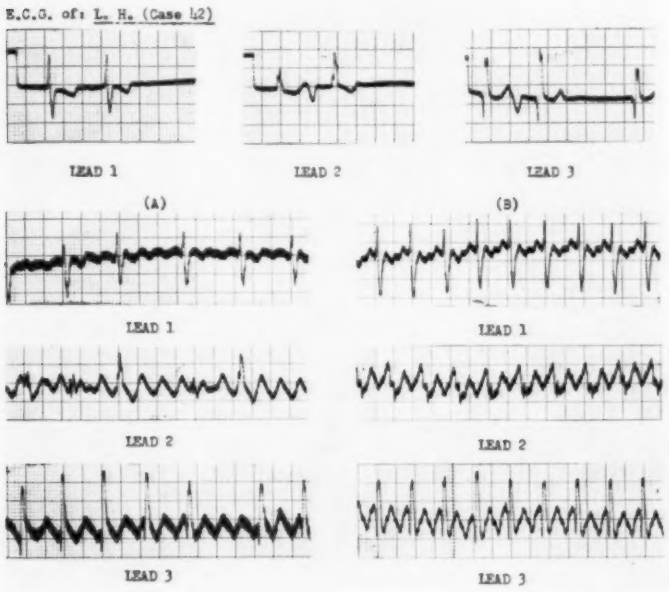

FIG. 3 (L. H. Case 42). In "A" the auricular flutter which developed while the catheter was in the right ventricle is seen in the three standard leads. In "B" although the catheter has been withdrawn, the auricular flutter with a 2 to 1 ventricular response is still present. This shortly reverted to a precatheterization pattern.

Auricular Fibrillation:

None of the patients of this series developed auricular fibrillation during cardiac catheterization. However, prior to this series, auricular fibrillation occurred in one patient during cardiac catheterization in this laboratory.

II. VENTRICULAR MECHANISMS

Premature Systoles:

The most common arrhythmia encountered during cardiac catheterization in this series was ventricular premature systoles which were seen in forty-four patients or 88% of the series. Ventricular premature systoles first appeared as the catheter tip approached the tricuspid valve. In many cases, the appearance of ventricular premature systoles was the first indication that the catheter tip had entered the right ventricular cavity. Similarly, ventricular premature systoles frequntly occurred when the catheter tip was withdrawn from the pulmonary artery or aorta into the right ventricle. As the catheter was advanced through the right ventricle, the configuration of the ventricular premature systoles changed indicating different foci of origin. The ventricular premature systoles arose from a single focus in only one patient (Case # 23). In numerous patients, ventricular premature systoles arose from both the right and left ventricle. This was also the experience of Lenègre and Maurice (11). However, Battro and Bidoggia (1), Duchosal et al. (5) and Sodi Pallares et al. (16, 17) report ventricular premature systoles arising from the right ventricle only. Hecht (7) describes ventricular premature systoles arising solely from the left ventricle during intracavitary studies of the heart. In the present series, the ventricular premature systoles arose mainly from the right ventricle. The occasional left ventricular premature systoles were usually seen when the catheter tip was in the region of the ventricular septum. Once the catheter had entered the pulmonary artery or aorta, ventricular premature systoles were rare, suggesting that the catheter tip is usually the stimulus for the arrhythmia.

Marcu, (14) studied ventricular premature systoles in the dog by passing electrodes into the right ventricle through the jugular vein and into the left ventricle through the carotid artery. He then produced ventricular premature systoles by electrical stimulation. In this way, he was able to prove that premature systoles from the left ventricle resembled right bundle branch block, while those arising in the right ventricle resembled left bundle branch block. He concluded that the Purkinje system was the chief source of ventricular premature systoles.

Stiffness of the cardiac catheter was a factor in increasing the frequency of ventricular premature systoles. This was apparent following the use of a new type of catheter which was particularly stiff. This fact stresses the importance of using catheters with proper flexibility.

Ventricular Tachycardia:

By definition, ventricular tachycardia is an uninterrupted series of three or more ventricular premature systoles. Ventricular tachycardia was a common arrhythmia during cardiac catheterization and was observed in thirty-nine patients in this series (78%). Except for case #38, ventricular tachycardia was seen only when the catheter tip was in the right ventricle and usually when the tip appeared to contact the ventricular septum. In case #38, short runs of ventricular tachycardia were seen as the catheter tip passed through the superior vena cava and right auricle. Cournand et al. (4) encountered ventricular tachycardia on several occasions. In one of their patients with a ventricular septal defect, the passing of the catheter through the defect produced ventricular ectopic beats of bizarre electrical configuration and short runs of ventricular tachycardia which ceased upon the withdrawal of the catheter into the right auricle. Levine et al. (13) and Sodi Pallares (17) have also encountered ventricular tachycardia in their intracavitary studies. There was no relationship between the occurrence of ventricular tachycardia during cardiac catheterization and the age of the patient or the type of heart disease in this series. The ventricular tachycardia usually consisted of short bursts of four to eight beats, but longer runs were occasionally recorded (Fig. 4). Figure 5 shows the effect of ventricular tachycardia on the right ventricular blood pressure. The ventricular tachycardia resulted in the fall of the systolic pressure from 55 to 19 mm. Hg. and a rise of the diastolic pressure from 12 to 15 mm. Hg. Usually ventricular tachycardia ceased with a change in the position of the catheter tip. However, in three cases (Case #21, 26, 48) ventricular tachycardia progressed into ventricular flutter and in one case (#1) into ventricular fibrillation before the cather could be withdrawn. For this reason, it is particularly important to observe the cardiac rhythm at all times while the catheter tip is in the ventricular cavity.

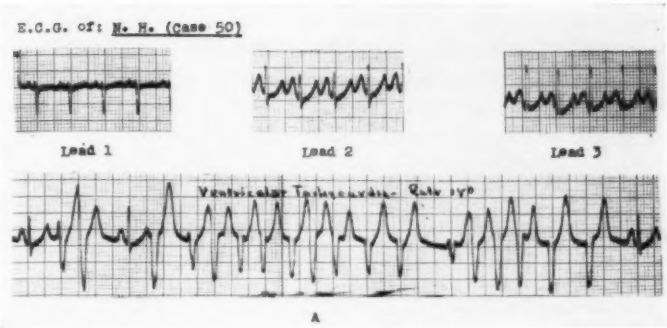

FIG. 4 (N. H. Case 50) illustrates a ventricular tachycardia at a rate of 180 per minute which appeared while the catheter tip was in the right ventricle.

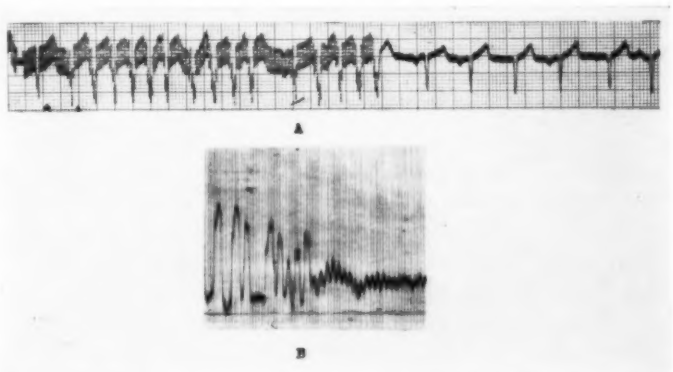

FIG. 5. "A" is an electrocardiographic tracing illustrating a rapid ventricular tachycardia which appeared while the catheter tip was in the right ventricle. The change to an auricular tachycardia with reversion to normal sinus rhythm occurred when the catheter tip was withdrawn into the right auricle. "B" is a pressure tracing taken with the catheter tip in the right ventricle at the onset of the ventricular tachycardia. The tracing shows the fall in right ventricular systolic pressure caused by the ventricular tachycardia.

Ventricular Flutter:

Ventricular flutter developed in three patients of this series. In case #21, a 7 year old white male with a patent ductus arteriosus,

numerous ventricular premature systoles and episodes of nodal tachycardia were present prior to cardiac catheterization. Consequently, in addition to morphine and scopolamine, the patient was premedicated with quinidine sulfate. When first seen in the laboratory, a sinus mechanism was present. However as the catheter was advanced into the right auricle, auricular and nodal premature systoles followed by nodal tachycardia appeared. As soon as the nodal tachycardia had reverted to a sinus mechanism, the catheter was advanced into the right ventricle where auricular and nodal premature systoles, and in addition short bursts of ventricular tachycardia were seen. The catheter tip was cautiously advanced through the right ventricular outflow tract, when ventricular flutter with a rate of 370 per minute suddenly appeared. The catheter was immediately withdrawn. The flutter persisted for approximately six seconds when it was replaced by nodal tachycardia which then reverted to a normal sinus rhythm (Fig. 2).

Case #26, referred by Dr. Robert Mason, was a 46 year old white male who had been digitalized because of rheumatic heart disease with mitral stenosis, auricular fibrillation and congestive failure. A patent ductus arteriosus was also suspected. Because of the possible active rheumatic myocarditis which would increase myocardial irritability, he was premedicated with 0.4 gm. of quinidine sulfate one and one half hours before catheterization. Upon passing the catheter, there was no change in the basic rhythm until the catheter entered the right ventricle when numerous ventricular premature systoles and several short runs of ventricular tachycardia appeared. Suddenly, a short run of ventricular flutter was seen, and the catheter was withdrawn into the right auricle. The flutter lasted for approximately three and a half seconds before reverting to the precatheterization pattern. Because of the extreme importance of establishing a definite diagnosis in this patient, a second attempt was made to enter the pulmonary artery which was successful. However, upon withdrawing the catheter tip into the right ventricle, another burst of ventricular flutter occurred. Though the catheter was immediately withdrawn, the flutter persisted for six seconds before reverting to a precatheterization pattern (Fig. 6). The flutter seen in this case was somewhat slower than the usual ventricular flutter since the rate was 220 per

minute. However, the electrocardiographic appearance was typical of ventricular flutter. This slow rate may have been due to the action of digitalis, quinidine or both. After the diagnosis of patent ductus

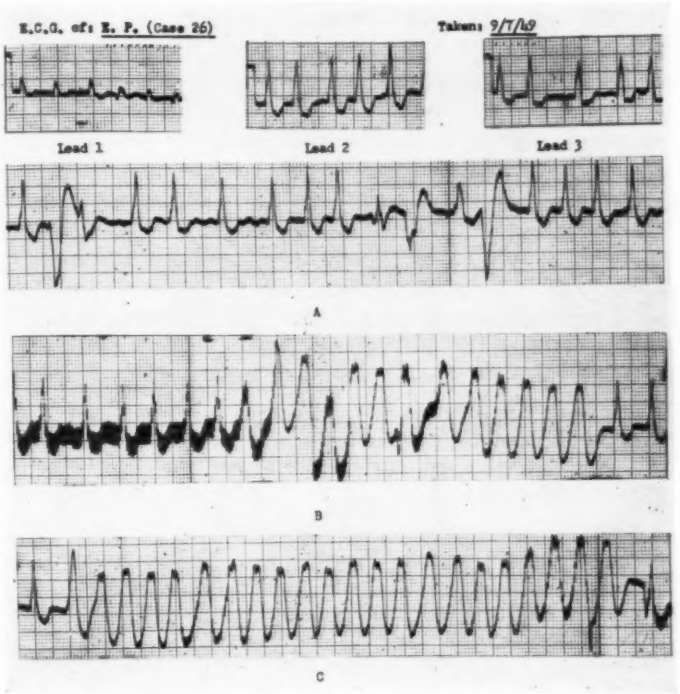

FIG. 6 (E. P. Case 26). "A" is a tracing of Lead 2 with the catheter in the right ventricle. A short burst of multifocal ventricular tachycardia is present. "B" and "C" are continuous tracings of Lead 2 with the catheter still in the right ventricle. In "B" a short run of ventricular flutter is present. In "C" a longer run of ventricular flutter which reverted to a precatherization pattern immediately upon the withdrawal of the catheter is seen.

arteriosus had been established, the ductus was ligated, and the patient made an uneventful recovery.

Ventricular flutter was again encountered in case #48, a thirty-six year old white female with an auricular septal defect. Auricular pre-

mature systoles and several short runs of auricular tachycardia appeared when the catheter tip entered the right auricle. Upon advancing the catheter into the right ventricle, numerous runs of ventricular tachycardia were seen. Suddenly, ventricular flutter appeared at a rate of 300 per minute which persisted for almost six seconds although

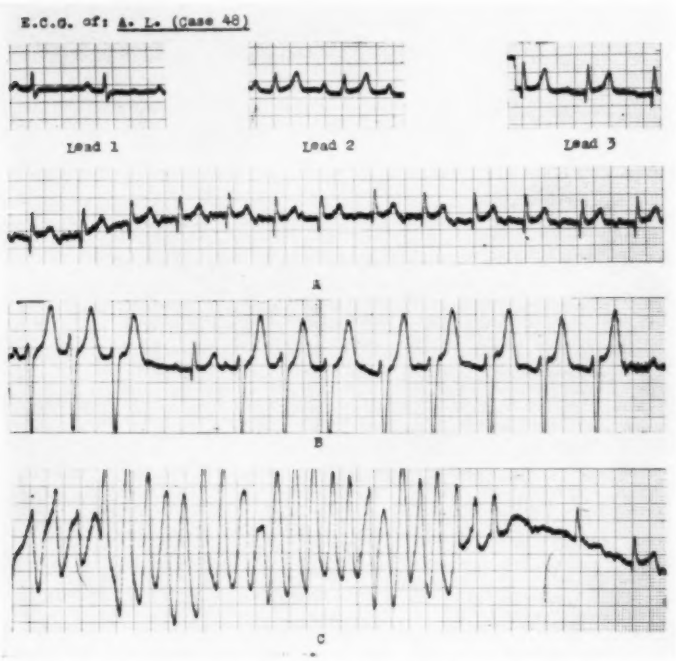

FIG. 7 (A. L. Case 48). "A" was taken with the catheter tip in the right auricle and presents numerous auricular premature contractions. "B" and "C" were taken with the catheter in the right ventricle. In "B" a slow ventricular tachycardia is present. An impure ventricular flutter at a rate of 285 per minute is seen in "C".

the catheter was withdrawn completely. This arrhythmia was not a pure flutter since certain portions of it resembled ventricular fibrillation (Fig. 7).

The fact that two of the three patients who developed ventricular flutter had a patent ductus arteriosus, is probably coincidental. In

this series, quinidine was used in only two cases, both of whom developed ventricular flutter. It is felt that quinidine did not predispose these patients to the development of ventricular flutter since the dosage used was well within the therapeutic range.

The occurrance of ventricular flutter in these three patients emphasizes the importance of electrocardiographic control during cardiac catheterization.

Ventricular Fibrillation:

Ventricular fibrillation has been encountered in only one patient studied in this laboratory. This patient (#1) was a ten year old white male who was referred to the Cardiac Clinic of the Harriet Lane Home for diagnosis of his cardiac abnormality. He had developed paroxysmal tachycardia at the age of three months, at which time a cardiac murmur was first heard. He continued to have repeated episodes of tachycardia and entered the clinic in congestive failure. The physical findings were limited to his cardiovascular system. There was no cyanosis. The heart tones were of poor quality, and a faint basal systolic murmur was present. Fluoroscopy revealed clear lung fields and enlargement of both the right and left ventricles. The electrocardiogram was reported as showing anomalous atrioventricular conduction (Wolfe, Parkinson, White Syndrome) (Fig. 8). The patient was digitalized and appeared to respond well to this therapy following which he was referred to this laboratory for cardiac catheterization.

The catheter was passed into the right auricle with ease. As it advanced into the right ventricle, ventricular tachycardia with a rate of 180 per minute appeared which then progressed into a rapid ventricular fibrillation. The patient became unconscious and had a convulsion. This entire process required only several seconds. The catheter was immediately withdrawn, and 0.4 gm. of quinidine lactate was given intravenously with no change in the pattern of ventricular fibrillation. A two percent solution of procaine hydrochloride was then given with no change. Meanwhile oxygen was administered first by anesthesia mask and then by intratracheal airway and positive pressure. A thorocotomy was performed exposing the heart, and cardiac massage was begun. Since intracardiac procaine followed by 0.8 gm. quinidine lactate proved ineffective, electric shock applied directly

to the myocardium was tried with no better results. The fibrillation gradually slowed and progressed to complete cardiac arrest (Fig. 8A, 8B).

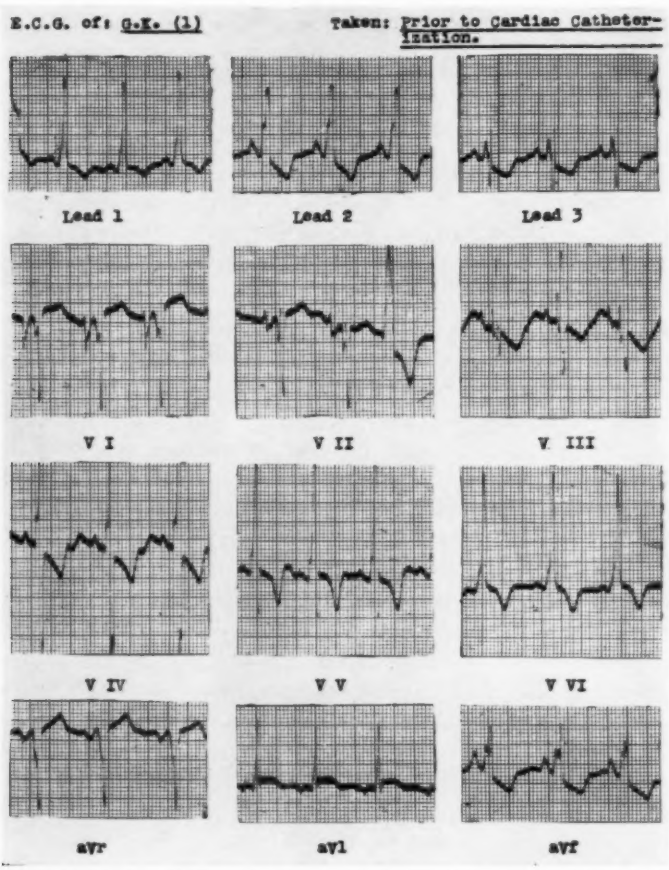

FIG. 8 (G. K. Case 1) illustrates the precatheterization pattern in case 1. Anomalous atrioventricular conduction is present.

The autopsy, performed by Dr. J. Burnett and J. R. Dunn, revealed a greatly hypertrophied heart with no congenital defects. Gross examination showed extensive myocardial and endocardial scarring of the

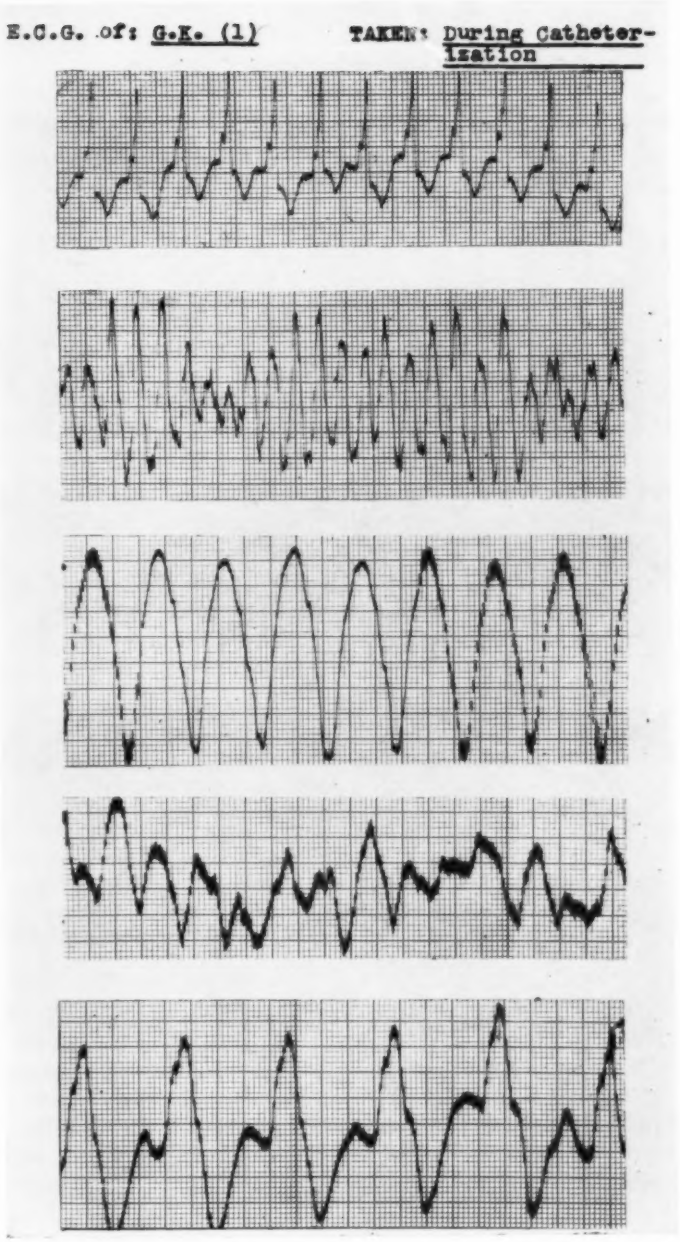

FIG. 8A (G. K. Case 1) shows the onset of ventricular tachycardia which progressed to ventricular fibrillation.

left ventricle which extended into the subepicardial and subendocardial ayers of the septum. The central cusp of the tricuspid valve was lessl pliable than usual and was fixed by short chordae tendineae to the

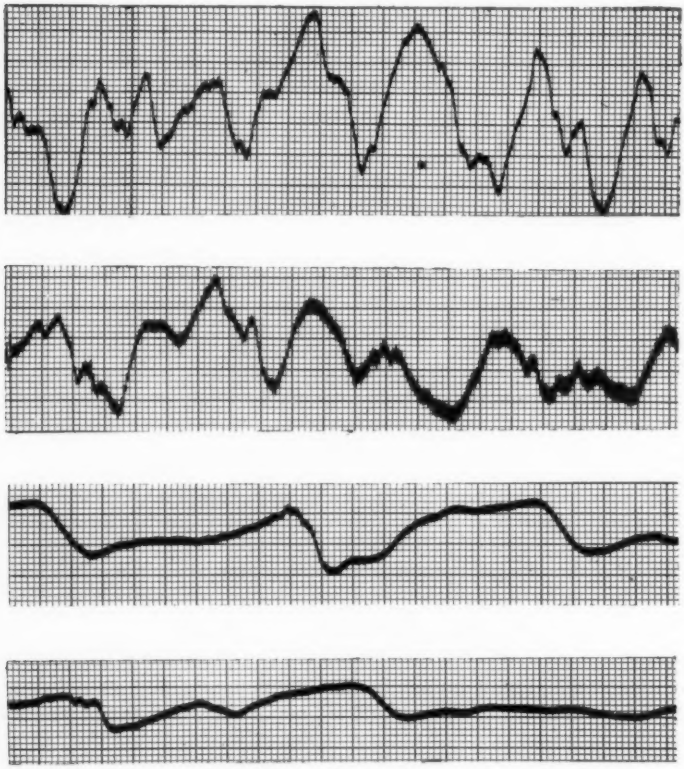

FIG. 8B (G. K. Case 1) shows the continuation of the ventricular fibrillation which developed in Figure 8A. The ventricular fibrillation gradually slowed and ended in cardiac standstill. Cardiac rhabdomyomatosis was found at autopsy.

area of subendocardial scarring probably causing a tricuspid insufficiency. The coronary arteries were thin walled and widely patent throughout. The microscopic diagnosis was thought to be either Von

Gierke's glycogen storage disease or rhabdomyoma of the myocardium. Following special studies and stains, the latter was felt to be the most likely diagnosis.

This was the first fatality encountered in this laboratory in over five hundred patients in whom cardiac catheterization had been performed.

III. CONDUCTION DISTURBANCES

Auriculoventricular Block:

Various degrees of auriculoventricular block developed in four patients in this series. First degree auriculoventricular block was seen in two patients (Case #11, 35). In the first of these, a patient with pulmonic stenosis and patent foramen ovale, the P-R interval was lengthened from 0.18 to 0.26 seconds while the catheter tip was in the right ventricle. This persisted for several minutes (Fig. 9). In case #35, a patient with primary pulmonary hypertension, the P-R interval increased from 0.12 to 0.20 seconds. Again the catheter tip was in the right ventricle, and the P-R interval reverted to its pre-catheterization time spontaneously. The development of first degree auriculoventricular block did not interfere with the progress of the catheterization.

Complete auriculoventricular dissociation developed in Case #41, a patient with Tetralogy of Fallot (Fig. 10). It appeared as the catheter was being advanced into the pulmonary artery. Upon withdrawal of the catheter into the superior vena cava, a normal sinus conduction pattern appeared which persisted despite further manipulation of the catheter. Only case #9, who had a Tetralogy of Fallot presented all three grades of auriculoventricular block (Fig. 11). Complete auriculoventricular dissociation occurred with the catheter tip in the inflow tract of the right ventricle. As the catheter was advanced through the outflow tract, the ventricular complexes became widened and slurred and showed multiplicity of origin. A pressure recording and blood sample were taken in the pulmonary artery following which the catheter was withdrawn into the superior vena cava. With the catheter in this position, auriculoventricular dissociation was replaced by a second degree then a first degree auriculoventricular block, and

finally a normal sinus rhythm appeared. Recatheterization of the right ventricle resulted in the same sequence of events. However, as the heart rate was normal, and the patient had no complaints, the catheterization was completed.

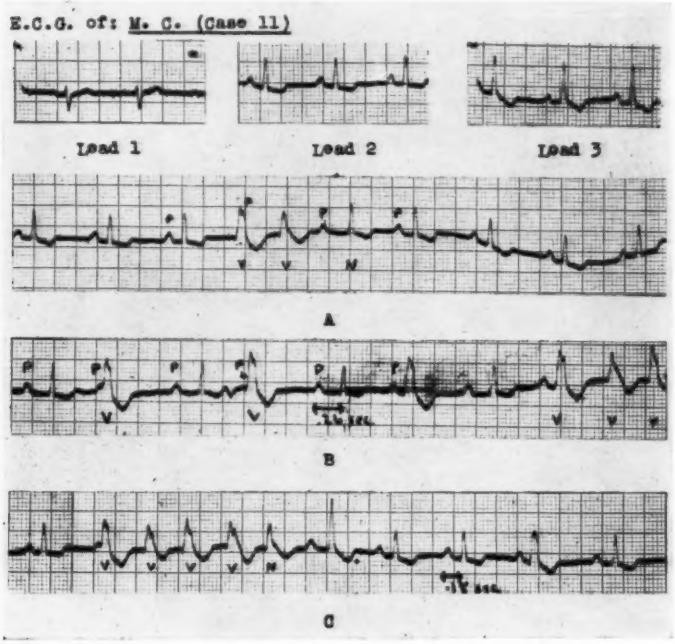

FIG. 9 (M. C. Case 11) "A", "B" and "C" are tracings taken with the catheter in the right ventricle. In "A", several ventricular and one nodal premature systole are seen. In "B", a transient first degree auriculoventricular block is present in addition to numerous ventricular premature systles. A short run of ventricular tachycardia followed by a nodal premature systole and return of the P-R interval to normal is seen in "C"

The various degrees of auriculoventricular block encountered in this laboratory were rapidly reversible and caused no subjective complaints. Hence, they did not interfere with the completion of the cardiac catheterization.

Bundle Branch Block:

Numerous investigators studying intracavitary potentials during cardiac catheterization have encountered transient right bundle branch block. Lenègre (11) reports such a mechanism occurring in a normal

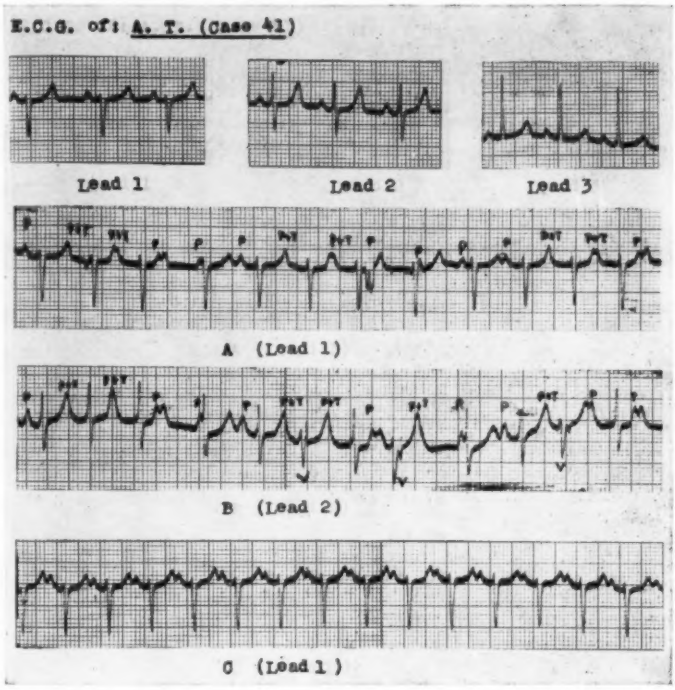

FIG. 10 (A. T. Case 41). "A", "B" and "C" were taken with the catheter in the right ventricle. "A" and "B" present a complete auriculoventricular block with an auricular rate of 150 and a ventricular rate of 120 per minute. Several ventricular premature systoles are present in "B". The block has disappeared in "C".

heart. Three cases are described by Sodi (17) two of which were complete and one incomplete. One of these cases, presenting transient complete right bundle branch block also had a normal heart. Kert and Hoobler (10) reported transient complete right bundle branch

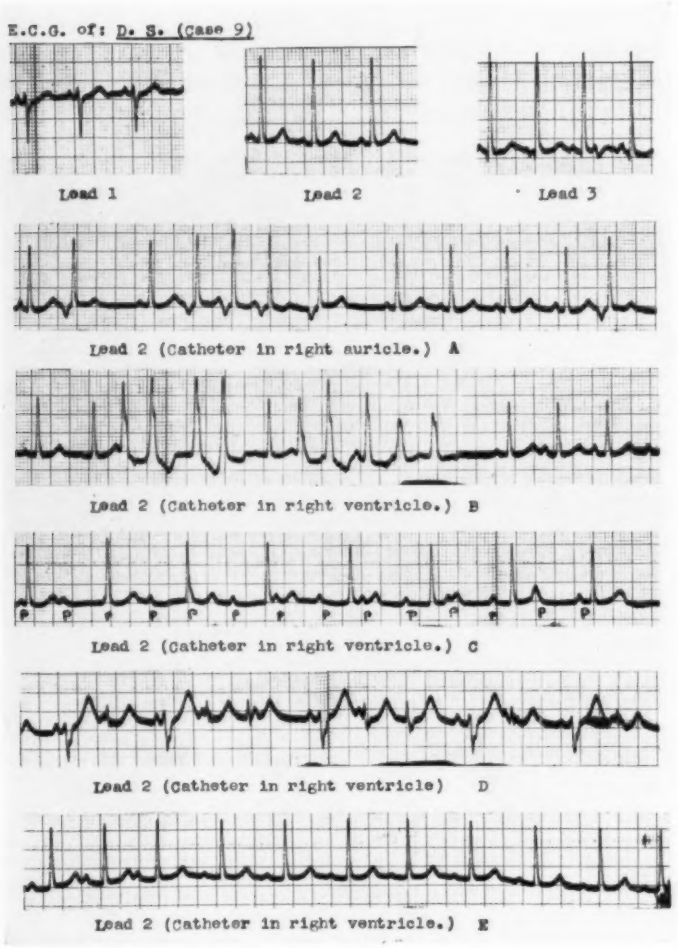
E.C.G. of: D. S. (Case 9)
Lead 1
Lead 2
Lead 3
Lead 2 (Catheter in right auricle.) A
Lead 2 (Catheter in right ventricle.) B
Lead 2 (Catheter in right ventricle.) C
Lead 2 (Catheter in right ventricle) D
Lead 2 (Catheter in right ventricle.) E

FIG. 11 (D. S. Case 9). In "A" numerous auricular premature systoles and a short run of auricular tachycardia are present. "B" presents two short runs of ventricular tachycardia. Complete auriculoventricular block has developed in "C". In "D", the ventricular complexes arise from two different foci. A first degree auriculoventricular block is present in "E".

block appearing during cardiac catheterization while studying a patient with hypertensive cardiovascular disease. They state that "pres-

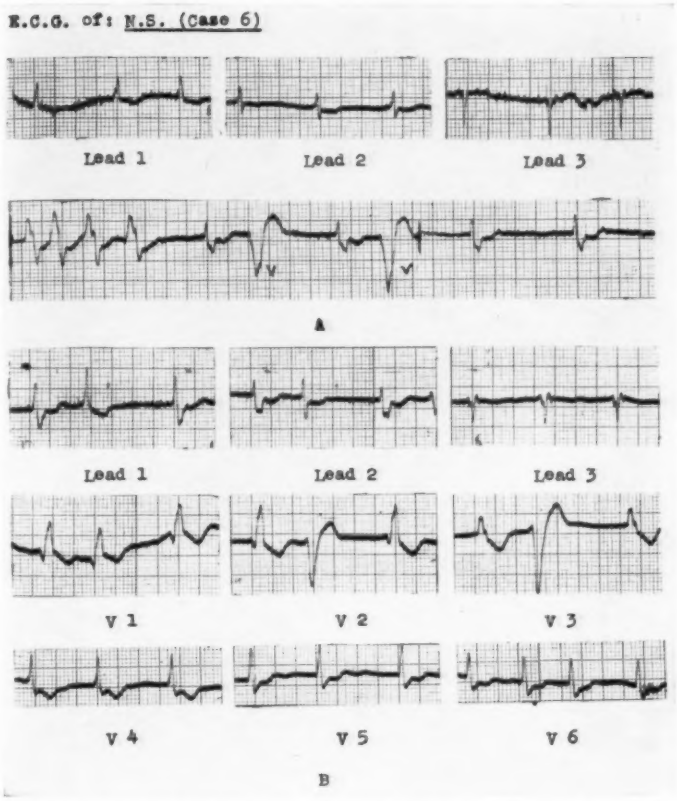

FIG. 12 (N. S. Case 6). "A" is a tracing of Lead 1 with the catheter tip in the right ventricle. A right bundle branch block has developed. A run of four ventricular premature systoles is also present. V illustrates ventricular premature systoles causing a bigeminy which persisted throughout catheterization and after the catheter was withdrawn. "B" is an electrocardiogram taken after the withdrawal of the catheter. The right bundle branch block which developed during catheterization is still present. However, occasional normal complexes are present in Lead 1 and Lead 2. Bigeminy is again present in V 2 and V 3. The sensitization in the V leads was 5 mm.

sure of the catheter against the endocardium may in some instances delay conduction in the right Purkinje plexus, in one of the subdivisions of the right bundle branch or in this structure itself".

Six patients (12%) in this series exhibited transient complete right bundle branch block at some time during cardiac catheterization.

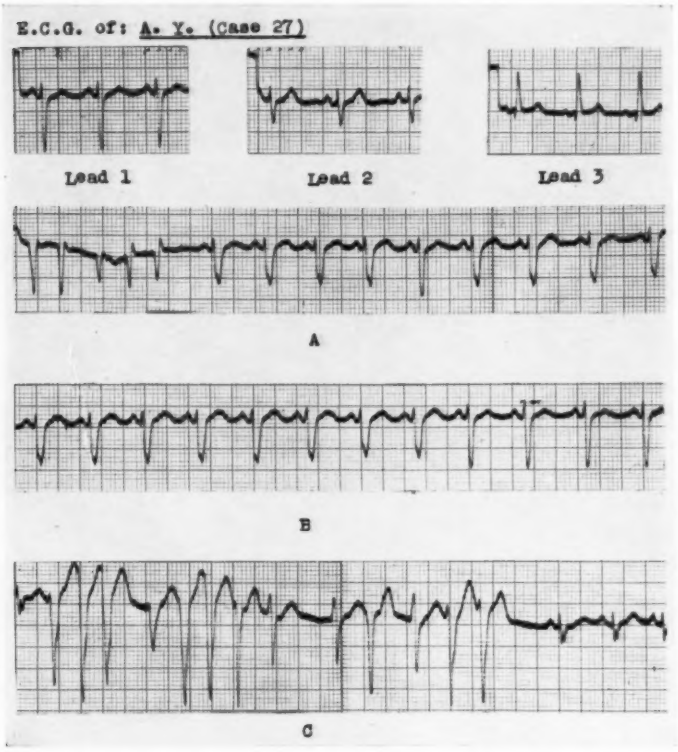

FIG. 13 (A. Y. Case 27). "A" and "B" are electrocardiographic tracings of Lead 1 taken with the catheter tip in the right ventricle. A right bundle branch block has developed in "A" following what appears to be a run of nodal tachycardia with aberrant conduction. The termination of the block is seen in "B". "C" is a tracing of Lead 2 taken with the catheter tip in the right ventricle. A ventricular tachycardia with an average rate of 200 per minute is present. An incomplete right bundle branch block is also seen.

One of these patients had hypertensive heart disease (#6), two pulmonic stenosis (#25, 46), one (#27) Eisenmenger's Complex, one

pulmonary hypertension (#35) and one had a patent ductus arteriosus (#47). Transient right bundle branch block always occurred with the catheter in the right ventricle and was of short duration except in case #6 in which the right bundle branch block was still present following the withdrawal of the catheter at the completion of the study (Fig. 12). In Figure 13, the beginning and ending of a transient complete right bundle branch block following a run of nodal tachycardia may be seen.

Transient right bundle branch block is not a serious arrhythmia during cardiac catheterization and never caused interruption of the study. Left bundle branch block secondary to cardiac catheterization has not been encountered in this laboratory.

SUMMARY AND CONCLUSIONS

The results of electrocardiographic observation throughout cardiac catheterization in fifty patients have been presented. All but one patient developed one or more types of cardiac arrhythmia.

Sixty percent of the patients developed auricular premature systoles. Nodal premature systoles were seen in seventy-eight percent. Supraventricular tachycardia of auricular or nodal origin occurred in twenty-eight percent and auricular flutter occurred in six percent.

Eighty-six percent of the patients in this series had ventricular premature systoles and seventy-eight percent developed short bursts of ventricular tachycardia. Ventricular flutter was seen in six percent of the patients. One patient developed ventricular fibrillation during cardiac catheterization with a fatal outcome.

Various degrees of auriculoventricular block occurred in eight percent of the patients during cardiac catheterization. Twelve percent developed transient right bundle branch block.

With the exception of one case, withdrawal of the catheter resulted in cessation of the serious arrhythmias encountered. Therefore, prompt recognition of the appearance of an arrhythmia is of great importance. This may be best accomplished by continuous electrocardiographic observation during cardiac catheterization.

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THE ANTIBACTERIAL ACTION OF NEOMYCIN AND FURADROXYL *IN VITRO* AND *IN VIVO*

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In a recent report from this laboratory (1) the antibacterial properties of eight antibiotics were compared. Since that time two other agents, neomycin and furadroxyl, have been received and have been studied in much the same manner as the first eight.

Neomycin is an antibiotic derived from a species of *Streptomyces*, similar to one isolated in 1916 by Waksman and Curtis (2) and named by them *S. fradiae*. Waksman and his associates (3, 4, 5) report that neomycin is a basic compound, most active in an alkaline environment, thermostable and soluble in water. It is effective *in vitro* against a number of gram positive and gram negative bacteria—notably the mycobacteria. Its antibacterial spectrum is similar to that of streptomycin, with the exception that streptomycin-resistant organisms are fully susceptible to neomycin. *In vivo*, these workers found that neomycin exerted a protective action in mice infected intraperitoneally with *Staphylococcus aureus* or *Eberthella typhosa* and in mice or chick-embryos infected with salmonellae. In the therapy of these experimental infections neomycin was superior to streptomycin. The neomycin used in the present study is the product of the Upjohn Laboratories and bears their number, 9084. It is a white to faintly cream-coloured material, presented in 0.25 gram lots.

Furadroxyl is a nitrofuran with the formula: 5-nitro-2-furaldehyde-2-β-hydroxyethyl semicarbazone. A 100 gram sample was received from the Eaton Laboratories, Inc., labeled Lab. Code No. NF 67, Control No. 196-15-1208. It is an orange-coloured crystalline preparation, soluble with difficulty in water to 100 mg per 100 ml. The only published report to date in which antibacterial properties of this

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agent are mentioned is that of Dreiser and his associates (6), who stated that it was bactericidal for *Lactobacillus acidophilus* at an undesignated concentration. Eaton and his associates (7) tested it against certain pneumonitis viral infections in mice and chick embryos. According to investigators in the Eaton Laboratories, Inc. (8), furadroxyl inhibits the growth of gram negative as well as gram positive bacteria.

METHODS

In vitro tests

The organisms tested were those collected for the previous study (1) with the addition of a strain of *Haemophilus influenzae* type B—No. 641—obtained through the kindness of Doctor Margaret Pittman of The National Institutes of Health. As before, the serial two-fold dilution technique was employed. The gram negative bacilli were tested in Difco heart infusion broth containing 0.05 per cent dextrose; for gram positive organisms 4 per cent rabbit's blood was added; *H. influenzae* was grown in Filde's medium. The routine inoculum was 0.5 ml of a 1:10,000 dilution of culture, except in the case of *H. influenzae*, growth of which was so scanty as to require the use of at least a 1:10 dilution. Aureomycin, streptomycin, polymyxin D and penicillin G were included in the tests as standards with which to compare neomycin and furadroxyl.

Therapeutic tests

CF_1 mice weighing about 20 grams were used. Infections were produced by the intraperitoneal injection of suitably diluted cultures of the C203 strain of Group A haemolytic streptococcus, the SV1 strain of pneumococcus type I, the KpnAD strain of *Klebsiella pneumoniae* type A and the strain of *H. influenzae* from Doctor Pittman.

The first three organisms were prepared for use in the manner described previously. *H. influenzae* cultures, grown on chocolate agar plates, were suspended in heart infusion broth and were so diluted in mucin as to result in approximately 350,000 organisms per ml. Mice were inoculated intraperitoneally with 1 ml amounts of this suspension.

Neomycin was compared with aureomycin in the infections induced with the streptococcus and the pneumococcus; with aureomycin and streptomycin in Friedlander's infections; and with aureomycin, streptomycin and polymyxin D in *H. influenzae* infections. The antibiotics were administered by the subcutaneous route in the doses indicated in the tables. Three treatments were given, the first immediately after injection of the micro-organisms, the second and third at 5½ and 23 hours respectively.

Because of the relative insolubility of furadroxyl it was decided to administer this drug by the oral route, incorporating it in the diet of the animals, as was the practice in testing sulfonamides (cf 9). Sulfadiazine was chosen as the standard of

comparison. From previous experience it was known that a 20 gram mouse eats about 4 grams of a drug-chow mixture during a 24 hour period. The drugs therefore were blended with Purina Dog Chow in proportions calculated to contain the daily dose in 4 grams. This worked out well for sulfadiazine but mice on the more concentrated furadroxyl diets ate less than the expected amount. In accordance with the early practice, the animals were placed on the diet—in order to accustom them to it—48 hours before they were to be infected and were maintained on it for 5 days after infection. The mice were kept in individual cages and their daily drug consumption was recorded. The amount consumed during the 24 hours before infection is shown in the table.

RESULTS

In vitro

In Table I are shown the least amounts of the agents which inhibited the growth of the micro-organisms for 20 hours. With longer incubation the end points of neomycin and furadroxyl rose by one or two tubes, but the change with time was never as great as that observed in the case of aureomycin (10). Minimal inhibitory concentrations of furadroxyl, at 20 hours, were greater than those of aureomycin for all of the organisms, whether gram positive or gram negative. They were greater than those of neomycin for the gram negative and gram positive bacilli and for staphylococci, but they were less for haemolytic streptococci belonging to Groups A, B and C and for the single strain of pneumococcus. Group D streptococci of both α and β varieties and streptococci of the viridans group were equally resistant to furadroxyl and neomycin.

Neomycin was in general more effective than aureomycin against gram negative bacilli. This was particularly true for strains of *Pseudomonas*, which are resistant to aureomycin, and strains of *Proteus*, most of which are resistant to both aureomycin and polymyxin. On the other hand, neomycin was much less effective than aureomycin against 18 of the 19 strains of streptococci, and the pneumococcus. One strain of *Streptococcus viridans* was more sensitive to neomycin. Staphylococci and gram positive bacilli were about equally sensitive to these two agents.

Except against strains of *Proteus*, polymyxin D has by far the greatest activity for gram negative bacilli of the agents studied here, while penicillin is the most effective agent against the cocci, again with an exception—the enterococci.

TABLE I

Minimal Inhibitory Concentrations of Furadroxyl, Neomycin, Aureomycin, Penicillin G and Polymyxin D

20-hour readings

ORGANISM	FURA	NEO	AUREO	POLY D
	Minimal inhibitory concentration, μg/ml			
E. coli #4	12.5	3.12	5	.156
Aerobacter #7	50	.78	5	.156
Aerobacter #8	>50	1.56	5	.312
K. pneumoniae A	25	.78	1.25	.156
K. pneumoniae B	50	.78	5	.625
Proteus #11	125	3.12	6.25	>500
Proteus #17	125	6.25	100	>500
Proteus #18	250	3.12	100	>500
Pseudomonas Herr	>500	7.8	100	2.5
Pseudomonas Beid	250	7.8	100	2.5
H. influenzae B	—	2.5	2	.35
				PENI G
Haem. Strept. Group A C203	6.25	25	.312	.008
A NY5	1.56	50	.078	—
A Cott	3.12	25	.078	—
B090	12.5	50	.625	.006
B19	6.25	50	.625	—
C K61	3.12	25	.156	—
D 22A	12.5	12.5	.625	2.5
D Bard	25	50	1.25	2.5
alpha Strept. faecalis Blak	25	50	.625	—
faecalis Tar	25	25	.625	—
viridans Keel	25	25	.625	—
viridans Dop	25	.312	.625	—
viridans Will	25	>50	.312	—
D. pneumoniae type I SVI	3.12	15.6	.312	.016
Staph. aureus Zorn	12.5	12.5	.625	.0625
aureus Gelb	6.25	.78	.625	.0625
aureus Gibb	12.5	.78	.625	—
aureus Barl	25	.39	.312	—
albus Heat	12.5	.625	.312	—
B. subtilis—Lederle	3.12	.078	.078	—
B. subtilis—FDA	3.12	.312	.156	—
"Diphtheroid" Green	50	.312	.156	—

TABLE II

Effect of Size of Inoculum on Titration End Points

DRUG	*E. coli* 84					*β streptococcus* C203				
	Inoculum = 0.5 ml. of dilution									
	1:5	1:500	1:10T	1:50T	1:5M	1:5	1:500	1:10T	1:50T	1:5M
	Endpoints μg/ml									
Neomycin	31.5	7.8	7.8	7.8	<3.9	200	200	25	25	12.5
Furadroxyl	50	25	12.5	12.5	6.25	>50	6.25	6.25	6.25	3.12

TABLE III

Therapy of Experimental Infections in Mice with Furadroxyl and Sulfadiazine

Rx: Oral, in diet, 2 days before and 5 days after infection

CONC. IN DIET, MG/100 GM	DRUG INTAKE* MG/MOUSE		PER CENT SURVIVAL (10 MICE EACH GROUP)			MEDIAN SURVIVAL TIME		
	Fura.	S.D.	Furadroxyl	Sulfadiazine	Controls	Furadroxyl	Sulfadiazine	Controls
			Group A β Streptococcal Infection Strain C203 50,000 MLD					
0	—	—	—	—	0	—	—	<24 hr.
25	—	1.1	—	90		—	>14 days	
50	2.1	2.3	0	100		<24 hr.	>14 days	
100	2.9	—	30	—		72 hr.	—	
			Type I Pneumococcal Infection Strain SVI 10,000–100,000 MLD					
0	—	—	—	—	0	—	—	31 hr.
50	2.1	2.1	0	0		36 hr.	48 hr.	
100	4.1	5.3	0	10		36 hr.	58 hr.	
150	5.5	6.2	0	0		38 hr.	76 hr.	
250	—	10.9	—	20		—	5 days	
			Type A *K. pneumoniae* Strain KpnAD 100,000–1,000,000, MLD					
0		—	—	—	0	—	—	<24 hr.
62.5	—	2.9	—	0		—	36 hr.	
125	4.2	5.1	0	10		<24 hr.	8 days	
187.5	5.9	—	0	—		<24 hr.	—	
250	9.0	10.4	10	100		<24 hr.	>14 days	

* Intake during 24 hours preceding infection.

Titration end points of neomycin and furadroxyl are affected by the number of bacteria inoculated, as shown in Table II. The increase in end point with increase in inoculum is of the same order of magnitude

as that observed previously (1) for aureomycin, chloromycetin, and penicillin but is less than that noted for polymyxin D which is especially sensitive to this factor.

In vivo

In the therapeutic trials furadroxyl was compared with sulfadiazine, the drugs being administered in the diet. The results, shown in Table III, are expressed as per cent survival and median survival time.

TABLE IV

Therapy of Experimental Infections in Mice with Neomycin and Aureomycin

Rx: Subcutaneous injections at 0, 5½ and 23 hours after infection

DOSE OF DRUG MG/KG/DOSE	PER CENT SURVIVAL (10 MICE EACH GROUP)			MEDIAN SURVIVAL TIME		
	Neomycin	Aureomycin	Controls	Neomycin	Aureomycin	Controls
	Group A β Streptococcal Infection Strain C203 50,000 MLD					
0	—	—	0	—	—	<24 hr.
4	—	10		—	76 hr.	
8	—	90		—	>14 days	
25	0	—		<24 hr.	—	
50	0	—		<24 hr.	—	
	Type I Pneumococcal Infection Strain SVI 10,000–100,000 MLD					
0	—	—	0	—	—	31 hr.
5	0	0		<24 hr.	60 hr.	
10	0	70		<24 hr.	88 hr.	
15	0	100		<24 hr.	>14 days	
25, 50, 100	0	—		33–36 hr.	—	

Since the maximum tolerated dose of furadroxyl, administered in a single dose by gavage, was found to be about 5.5 mg per mouse (11), treatment with this agent was limited to 10 mg per day or less. Furadroxyl was less effective than sulfadiazine in protecting mice. Prolongation of life, as compared with the controls, was noted with furadroxyl only in the case of the streptococcal infection. Administration of sulfadiazine, even at levels which failed to save any of the mice, increased their median survival time by at least one-half day.

Neomycin, as might have been predicted from the *in vitro* tests, was ineffective against the streptococcal and pneumococcal infections, failing even to increase survival time, in doses up to 50 or 100 mg per kg per treatment (see Table IV). It showed considerable activity, however, against infections induced with gram negative bacilli (Table V). It was more effective than aureomycin or streptomycin against the strain of *K. pneumoniae* and was as effective as aureomycin

TABLE V

Therapy of Bacillary Infection in Mice with Neomycin, Aureomycin, Streptomycin and Polymyxin D

Rx: Subcutaneous injections at 0, 5½ and 23 hours after infection

DOSE OF DRUG MG/KG/ DOSE	PER CENT SURVIVAL (10 MICE EACH GROUP)					MEDIAN SURVIVAL TIME				
	Neo	Aureo	Strepto	Poly D	Controls	Neo	Aureo	Strepto	Poly D	Controls
	Type B H. *influenzae* Infection Strain 641 10–100 MLD									
0	—	—	—	—	10	—	—	—	—	<24 hr.
1	30	30	80	90		<24 hr.	<24 hr.	>8 days	>8 days	
5	40	70	100	90		<24 hr.	>8 days	>8 days	>8 days	
20	80	80	90	100		>8 days	>8 days	>8 days	>8 days	
80	90	—	—	—		>8 days	—	—	—	
	Type A *K. pneumoniae* Infection Strain KpnAD 100,000–1,000,000 MLD									
0	—	—	—		0	—	—	—		<24 hr.
0.5	0	—	—			38 hr.	—	—		
1	70	—	—			>14 days	—	—		
2	90	—	40			>14 days	—	5 days		
5,10	100	—	—			>14 days	—	—		
50	—	30	—			—	66 hr.	—		
100	—	90	—			—	>14 days	—		

against *H. influenzae*. Streptomycin and polymyxin D were more effective than either neomycin or aureomycin in this last infection, the difference between survival rates for aureomycin and streptomycin, at the 1 mg/kg/dose level, being statistically significant, with a probability of .018. It is interesting that at doses which protected less than half the mice there was no increase in survival time over that observed in the controls. Ninety-five per cent of the animals that died did so in the first 24 hours.

DISCUSSION

From the *in vitro* tests one might expect furadroxyl to show considerable activity against infections. Former studies gave 800, 80 and 1500 μg/ml as the minimal inhibitory concentrations of sulfadiazine for C203, SV1 and *E. coli*, in tests carried out in broth. Inhibitory concentrations of furadroxyl for these same organisms were 6, 3 and 12 μg/ml. Yet furadroxyl was decidedly less effective than sulfadiazine in protecting mice infected with the streptococcus, the pneumococcus and a strain of *K. pneumoniae*. Failure of a drug to live up *in vivo* to its *in vitro* promise can usually be ascribed to unfavorable pharmacological behaviour, including toxicity, or to inactivation in the body. Since Eaton and his associates found furadroxyl effective in controlling viral infections in mice neither of these explanations seems likely—unless one assumes that altered furadroxyl, while inactive for bacteria, still possesses antiviral properties. It is pertinent, in this connection, that Paul and his associates (12) found unaltered furadroxyl in the urine of rats fed the drug, but only to the extent of 20% of the amount administered.

Compared with aureomycin, neomycin was ineffective *in vivo* as well as *in vitro* against the haemolytic streptococcus and the pneumococcus. Against *H. influenzae* these two agents were equally effective, both *in vivo* and *in vitro*. With *K. pneumoniae*, however, a discrepancy is noted between *in vivo* and *in vitro* behaviour. Aureomycin and neomycin inhibit *K. pneumoniae* in the test tube at approximately the same concentration, but neomycin is appreciably more effective in protecting mice against this organism.

While neither neomycin nor furadroxyl revealed exceptional antibacterial activity, neomycin has one advantage over the other antibiotics that have been examined in this laboratory, namely its potency for strains of both *Proteus* and *Pseudomonas*. In a previous paper (1) attention was called to the fact that agents derived from streptomyces ordinarily possessed activity for the first of these organisms but not for the second, while antibiotics of bacterial origin behaved in the opposite manner. It was suggested that this difference reflected a fundamental difference in the mode of action of the two kinds of antibiotic. If this is so, neomycin must exert its effect through still another mechanism.

SUMMARY

Furadroxyl was, in general, more effective against gram positive than gram negative bacteria but against all bacteria it was less active *in vitro* than aureomycin. In therapeutic trials in mice it was less effective than sulfadiazine.

Neomycin was as effective as aureomycin, *in vitro*, against gram negative bacilli of the coli-aerogenes group, *H. influenzae*, straphylococci and gram positive bacilli. It was the more effective of the two against strains of *Proteus* and *Pseudomonas*, in fact it is the only antibiotic studied in this laboratory that is potent for both of these organisms. Neomycin was less active than aureomycin in inhibiting the growth of streptococci. *In vivo*, it gave better protection than aureomycin to mice infected with *K. pneumoniae* and was as effective as aureomycin in the therapy of *H. influenzae* infections. In infections with the haemolytic streptococcus and the pneumococcus, however, neomycin was valueless.

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ANTIMONY CONCENTRATION IN THE THYROID GLAND AND ITS EFFECT UPON METABOLIC RATE AND SERUM CHOLESTEROL LEVEL[1]

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In view of the reports of Maren and Otto (1) and of Cowie et al. (2) concerning the localization of antimony in the thyroid gland of the dog, it seemed pertinent to investigate the localization of antimony in the thyroid gland of the rabbit and any possible effect on thyroid function which might be reflected in the body weight, oxygen uptake or serum cholesterol level. The rabbit seemed particularly well suited for such a study since it has been shown that thyroidectomy is followed by a sharp rise in the serum cholesterol concentration and a gradual drop in the metabolic rate (3).

METHODS

Six male albino rabbits were injected intravenously once a day for 21 days with one mg. of antimony per kg. body weight in the form of tartar emetic. Five male albino rabbits which remained untreated served as controls.

Oxygen consumption was measured with the apparatus described by Tainter and Rytand (4) with the modifications suggested by Fleischmann, Shumacker and Wilkins (5). The serum cholesterol concentration was determined by the procedure outlined by Peters and Van Slyke (6).

The animals were autopsied 48 hours after the last injection of antimony and specimens removed for histologic study and chemical analyses. The specimens for histologic study were fixed in Zenker's fluid and stained with hematoxylin and eosin. The antimony concentration of the tissues was estimated with rhodamine B using the method described by Maren (7).

RESULTS

The results of this study are summarized in Table I. It can be seen that during the pre-injection period of seventeen days there was no difference in the body weight, oxygen uptake or serum cholesterol level of the animals selected for treatment and those which remained

[1] This study was supported in part by the Commonwealth Fund.

as controls. During the twenty-one day treatment period there was no significant change in the serum cholesterol level of either group. There was a slight fall in the average oxygen consumption of both the treated and control group. The animals injected with antimony showed an average body weight lower than that of the controls and in fact lower at the end of the treatment period than at the beginning.

The results of the chemical analyses for antimony in the tissues are given in Table II. No antimony was found in the tissues of the un-

TABLE I

Effect of antimony injections on oxygen uptake, serum cholesterol level and body weight

GROUP	PERIOD	OXYGEN UPTAKE	SERUM CHOLESTEROL	BODY WEIGHT
		cc./kg./hour	*mg./100 cc.*	*gm.*
Antimony	Before injection	579 (442–700)	51.4 (39–68)	2537 (2315–2705)
Antimony	After injection	529 (425–671)	51.8 (26–94)	2435 (2285–2575)
Control	Before injection	607 (442–739)	50.8 (35–60)	2531 (2235–2685)
Control	After injection	538 (469–687)	44.5 (24–84)	2761 (2715–2825)

TABLE II

Concentration of antimony in various tissues

TISSUE	ANTIMONY CONCENTRATION (MICROGRAMS ANTIMONY PER GRAM OF WET TISSUE)
Thyroid	29.9
Liver	30.2
Spleen	6.0
Muscle	2.9
Kidney	2.3
Lung	0.7

treated animals. The figures in Table II are based on the average of six determinations except in the case of the thyroid where only two analyses were performed, the other specimens being used for histologic study.

Dr. Morgan Berthrong, Resident Pathologist of the Johns Hopkins Hospital, was kind enough to examine the microscopic sections. He was unable to detect any difference between the thyroid glands of those animals injected with antimony and those which served as controls.

DISCUSSION

Antimony administered in a dose of one mg. per kg. of body weight appeared to have some toxic action since the weight of the injected animals fell while the weight of the control animals rose. However there was no significant alteration of the oxygen consumption or serum cholesterol level. The antimony concentration of the thyroid and liver was ten times as high as that of the muscle and kidney and five times as high as that of the spleen. The absence of histologic changes in the thyroid gland is consistent with the absence of any demonstrable change in thyroid function.

SUMMARY

The thyroid gland of the rabbit has been shown to accumulate antimony in appreciably higher concentration than that of the other tissues with the exception of the liver. Under the conditions of this experiment the accumulation of antimony by the thyroid gland did not influence its physiologic activity or histologic structure.

ACKNOWLEDGEMENTS

The author wishes to express his thanks to Mr. Thomas Maren, Dr. Roger A. Lewis, Dr. Morgan Berthrong, and Dr. Lawson Wilkins for their aid and encouragement.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Bulletin)

Physiology of Heat Regulation and the Science of Clothing. Edited by L. H. NEWBURGH. 457 pp. $7.50 *W. B. Saunders Co., Philadelphia, Pa.*

Just prior to our entry into World War II, the American Institute of Physics sponsored the publication of an exhaustive handbook entitled *Temperature: Its Measurement and Control in Science and Industry.* The extent of information available in this volume on many aspects of temperature was staggering in its scope. Nevertheless, military strategy of the past war placed men in machines and in locations where the environmental stresses evoked by temperature were so severe that the problems to be solved required information which simply was not known. The losses of efficiency as well as casualties from exposure to extreme heat and cold constituted a major strategic problem in several theaters and in all the forces. In an attempt to measure the fundamental processes involved and to devise protective measures a large number of skilled investigators devoted much time to both the basic and practical problems which arose. As a result there accumulated in the course of five years a wealth of information, much of which was scattered or buried in classified reports to responsible governmental agencies.

Now under the sponsorship of the Division of Medical Sciences, National Research Council, these accumulated observations have been integrated and presented in this present handbook. The list of authors establishes immediately the high caliber of the contributors who have undertaken to review interpretatively the mass of data available in the field in which they are expert. Drs. H. C. Bazett, R. Day, J. D. Hardy, L. P. Herrington, Sid Robinson, C. R. Spealman and C. P. Yaglon each has written on an aspect of the Human Response to the Climatic Environment. This section is introduced by Dr. F. R. Wulsin in an extensive description of adaptations to climate among non-European peoples. Lest this latter topic appear pedantic, it may be pointed out that most of the *principles* of adaptation to climatic stress which are employed presently are mainly technical improvements on methods developed by such non-European peoples as Eskimo, Mongols, Fuegians, Bedouins and Javanese.

The second section is devoted to the topic of Clothing, a Thermal Barrier. The contributors include Drs. E. A. Adolph, H. S. Belding, R. Day, M. A. van Dilla, W. H. Forbes, L. Fourt, M. Harris, S. Robinson, P. A. Siple and C. R. Spealman. Here, in close relation to the related physiological phenomena, is set forth the biophysics of the many-facetted and difficult field of clothing.

All concerned with the publication of this book should enjoy the satisfaction of having completed an important review which records basic advances in a special but important field to which the authors themselves have made outstanding

contributions. Anyone concerned with the biological aspects of temperature will find this book invaluable.

J. L. L., Jr.

Clinical Electroencephalography. By ROBERT COHN. 639 pp. $14.00 *McGraw-Hill Book Co. Inc., New York.*

The young specialty of electroencephalography has rapidly developed during the past decade in spite of the fact that dissemination of knowledge in the field was largely by word of mouth. It is, then, pleasing to have a monograph written for clinicians, who are more interested in the application of the technique to bedside problems, than in the biophysical mechanisms involved in the tracings.

After a brief discussion of the origins of cerebral potentials and the characteristics of waves, the author discusses the techniques used in human recording. The importance of personal supervision of the examination is stressed if a complete interpretation of the record is to be made during a single test. The tyro in the field would appreciate a more detailed account of artifacts which are always troublesome and the expert will miss a discussion on special electrodes—pharyngeal, tympanic, etc.—and on special activating techniques—metrazol, photic stimulation, etc.

The clinical material is concisely and clearly presented along with samples of the electroencephalograms and the interpretation. The findings in most of the common neurological diseases affecting the brain are described and illustrated in some 273 plates. The format of the clinical and electroencephalographic presentations is both pleasing to the eye and easy to comprehend. A statistical analysis of the electroencephalographic findings in the common diseases should be of value to the beginner wishing to compare his "score" with a "norm".

The references are selected and hence too few to be of much value to a critical student in the field. The index is adequate.

This monograph represents a distinct contribution to the medical profession and to those interested in nervous activity. It has a special appeal for all neurologists, neurosurgeons and psychiatrists, and should be a valuable reference work for every student of the nervous system.

A. E. W.

Physiology of the Uterus, 2nd edition. By S. R. M. REYNOLDS. 611 pp. $12.50. *Paul B. Hoeber. Inc. New York.*

The appearance of the second edition of "The Physiology of the Uterus" after a ten year interval will be welcomed not only by the physiologists but by the obstetrician and gynecologist as well. Especially for the clinical group this volume will prove a gold mine of information hitherto obtainable only from widely scattered sources.

This has been no mere perfunctory revision of the previous work. One hundred and fifty pages and twenty-three illustrations have been added. The already large list of references has been nearly doubled. The most obvious change, as the author suggests in the preface, is one of organization. Instead of a division into thirteen chapters, as in the first edition, the book is divided into eight major sections, each

containing several closely related chapters. The pertinent bibliography is found at the end of each section, facilitating reference to it.

The author's own work in the field of uterine physiology has been outstanding, and its inclusion in the new chapters on Human Tokography, Uterine Vascular Adaptations to Pregnancy, and in the expansion of the chapter on uterine growth during pregnancy, would alone make the reading of this volume an educational experience. In this latter chapter, the conversion of the uterus from a spheroid to a cylinder during the course of pregnancy is described as a factor in adaptation not only to fetal growth but to fetal maturity at term. This concept is entirely new and may yet have far-reaching clinical results. The chapter on steroid hormones, which is new, is a clear cut summary of current knowledge in this field, while the expanded chapter on menstruation is, without reservation, excellent.

A chapter dealing with placental exchange contains a fair review of the current work with tracer substances but is less detailed than expected when it deals with the transfer of specific substances, such as vitamins and toxins.

The section on innervation has been the least worked over, perhaps because less progress has been made in this particular field. However, the omission of the work of Cleland on the pathways of uterine pain, and its repeated confirmation by the use of various extradural blocks during labor, does not seem reasonable.

There are certain minor and unimportant errors mostly related to clinical obstetrics, such as the statement that the blood volume increases only 10 to 15 percent during pregnancy or that vitamin K can be used for the control of postpartum hemorrhage. By and large, however, the volume fulfills well its objectives, to be a storehouse of fact and reference; to serve as a stimulus for, and a director to, work yet undone. One cannot close this review without a word of praise to the publishers for a superb example of medical book making.

L. M. H.

General Endocrinology. By C. Donnell Turner. 604 pp. $6.75. *W. B. Saunders Co. Philadelphia, Pa.*

Endocrinology has progressed at such a rapid pace that at present it can scarcely be covered adequately in a single book. The physician requires a text which shows him how to apply the newer knowledge toward the better understanding, diagnosis and treatment of the various clinical syndromes. For this purpose it is necessary that he be oriented concerning the relations of the endocrine glands, the physiologic action of the hormones and the application of laboratory methods of study. On the other hand, for the student or investigator who wishes to delve deeper into the fundamental scientific background of endocrinology, the experiments upon which present theories are based must be described and evaluated and the numerous unsolved problems and differences of opinion which exist today must be discussed. In the latter respects GENERAL ENDOCRINOLOGY written by C. Donnell Turner of the Zoology Department at Northwestern University is a valuable contribution.

In this volume of 604 pages endocrinology is approached from the experimental rather than a clinical point of view. The characterization and treatment of clinical

endocrinopathies are not emphasized but, whenever possible, the human being has been chosen to illustrate the operation of biologic principles. The rather complicated subject is discussed in an unusually clear and concise manner. The volume is well illustrated with original charts and diagrams. The recent knowledge concerning the physiology and chemistry of the hormones was well up to date at the time of publication. The author gives careful consideration to divergent and unproved hypotheses. The annotations and the references at the end of each chapter furnish an excellent bibliography of the more important and recent articles on the subject. Naturally, there are some omissions and probably some inaccuracies in the presentation of such a vast subject. Although the book is admittedly written for zoologists, the reviewer does not hesitate to recommend it enthusiastically for medical students and physicians who desire a thorough but concise discussion of the basic knowledge of endocrinology.

L. W.

Minutes of the Seventh Streptomycin Conference, Held in April 1949 in Denver, Colorado. 360 pp. Prepared and Edited by Veteran's Administration Area Office, Washington, D. C.

A vast study of the chemotherapy of tuberculosis has been undertaken by the Veteran's Administration, the Army, Navy, U. S. P. H. S., and various civilians. In all some 54 hospitals have been cooperating in this effort. The present publication consists of the minutes of the seventh semi-annual conference, at which the participating investigators summarized and appraised the results.

The majority of the papers may be placed under these general headings: the emergence of resistance of tubercle bacilli to drugs; the effect of streptomycin upon pulmonary and extra-pulmonary tuberculosis; the use of streptomycin in the surgery of the tuberculous patient; the pharmacology and therapeutic trial of para-amino-salicylic acid. The discussion of the streptomycin-resistant organisms is the most valuable portion of this publication, and produces much interesting data, though no solution, of this chemotherapeutic dilemma.

The sections on therapeutic trials are disappointing. The opportunity for a definitive study of the usefulness of streptomycin has clearly been lost. Failure to employ the usual techniques of impartial drug-testing has produced a great mass of isolated data, which is difficult if not impossible to evaluate. This is especially true of the material on pulmonary tuberculosis, and one cannot decide from the data as it appears in print, whether streptomycin has any effect upon the progress of the disease. In regard to extrapulmonary tuberculosis, immediate improvement after streptomycin therapy seems definite in a majority of cases, although the long-term results are less easy to assess. Effectiveness of streptomycin in meningitis and miliary tuberculosis is unquestionable, since about one-third of the patients survive, a fraction less glowing than early reports, but substantial nonetheless.

It is unfortunate that so much hard work has resulted in data that cannot be interpreted. Perhaps this is because of the modest effectiveness of streptomycin in tuberculosis, or perhaps the very size of the study defeats its purpose. One

suspects however that the fault lies in the plan of the experiment, since the British in a recent publication have beautifully demonstrated the effectiveness of streptomycin in a careful study of 107 cases of pulmonary tuberculosis.

C. G. Z.

Antibiotics. Edited by GEORGE W. IRVING, JR. and HORACE T. HERRICK. 273 pp. $6.75. *Chemical Publishing Company, Inc., Brooklyn, N. Y.*

The Graduate School of the United States Department of Agriculture presented a series of talks on antibiotics during the period of September 1946 to January 1947. These have now been published in book form. While the material was quite timely in 1946, the delay in publication has exacted its usual penalty. The lecturers represent an imposing list of many of the active investigators in the development of antibiotics. The topics constitute an excellent resumé of the state of knowledge of antibiotics in 1946. In addition there is valuable source material, of a kind sometimes hard to locate quickly, in the last four lectures, namely: "Chemistry of Antibiotics Other than Penicillin, Streptomycin and Gramicidin", by Dr. Wintersteiner; "Basidiomycetes as Possible Source of Antibiotics", by W. J. Robbins; "Antibiotics from Higher Plants", by G. W. Irving, Jr., and "Antibiotics in Veterinary Medicine", by J. O. Heishman.

The limitations of the book are largely those of omission of the developments of recent years. Thus aureomycin and chloramphenicol are not included, and there is nothing about the chemistry of mechanism of action of the penicillins. Finally, clinical applications have been surveyed rather rapidly by Dr. Keefer, and moreover the concepts of dosage have undergone some metamorphoses since his talk was given. These lectures will therefore appeal to those working in the antibiotic field rather than to the clinician.

C. G. Z.

Normal Values in Clinical Medicine. By F. WILLIAM SUNDERMAN and FREDERICK BOERNER, 845 pp. $14.00. *W. B. Saunders Co.*, Philadelphia, Pa.

There has always been a need in the medical literature for a compendium of data comparable to that published annually in *The Handbook of Chemistry and Physics*. Such a text has now been published under the editorship of Dr. F. William Sunderman and Dr. Frederick Boerner. The "normal" values for a wide variety of biological and chemical properties of human beings have been compiled with the aid of a large group of collaborators. The subject matter covered is wide, and is as all-inclusive as one could possibly expect in a first edition.

Certain shortcomings of this book are soon apparent. A failing, well-recognized by the editors, is the frequent use of too few observations in the calculation of the norm. Normal value for certain chemical constituents are listed without any critique of the methods employed. For example, no explanation is offered for the four-fold difference in the "normal" concentration of copper in serum, as determined by different methods. Methods, indeed, are usually not described, though reference is freely made to original sources. This seems adequate where no division of opinion is reported. Finally, "normal" values cited for the same chemical substance differ in different sections of this book. For example, the "normal" values of bilirubin and total cholesterol differ in Tables 117 and 169. The value for the

concentration of fibrinogen in plasma differ on page 109 and Table 169, and the "normal" value for an oral galactose tolerance test is recorded differently on page 145 and 273.

Fortunately, the book includes many miscellaneous data such as compilations of food values, a section on statistical methods, and some posologic and actuarial information. The latter are not useful, since separate tables for males and females are not presented.

Despite its inadequacies, this is a book to be welcomed. Unfortunately, the format is elaborate, and the book expensively printed. The data assembled are largely ephemeral. A less expensive handbook, more compactly written and printed, which could be reprinted at intervals of 1 or 2 years, would seem to be in order.

O. D. R.

Clinical Diagnosis by Laboratory Examinations, 2nd edition. By JOHN A. KOLMER. 1212 pp., $12.00. *Appleton-Century-Crofts, Inc. New York.*

The second edition of this book closely resembles the first, but new material has been added and some sections have been revised. Emphasis is placed on interpretation of laboratory tests rather than on techniques. The tremendous amount of material covered has resulted in a rather superficial and uncritical discussion of the individual subjects. The frequency with which a given laboratory test gives positive results in various disease states is rarely mentioned. One is often unable to determine by reference to this book whether or not the results of a test are of specific diagnostic significance or only of academic interest. While the volume is as satisfactory as other contemporary works on the subject, it again demonstrates the inability of a single author to keep abreast of new developments in all fields of medicine.

C. L. C.

An Atlas of the Blood and Bone Marrow. By R. PHILIP CUSTER. 321 pp. $15.00. *W. B. Saunders Co., Philadelphia, Pa.*

Of the several atlases of hematology available, this volume is unique because of the variety of material presented. There are 285 illustrations, the great majority of which are large and beautifully reproduced photographs of the blood and marrow at high magnification. Some of these photographs are in color. The most valuable feature of the book is the presentation, often side by side, of reproductions of both smears and of fixed tissue sections of marrow in the various blood dyscrasias. The illustrations are supported by concisely written textual discussions which are remarkable for their accuracy and clarity. This book is an outstanding contribution to the hematologic literature and should be available to every physician and pathologist concerned with the examination of the blood and bone marrow.

C. L. C.

Essentials of Obstetrical and Gynecological Pathology, 2nd Edition. By ROBERT L. FAULKNER and MARION DOUGLASS. 357 pp. $8.75 *The C. V. Mosby Co., St. Louis, Missouri.*

This monograph represents an enlargement of a very fine first edition on the subject of obstetrical and gynecological pathology. The total number of illustra-

tions has been increased and the quality of these illustrations greatly improved. As the authors point out in the preface, the teaching of special pathology has become of major importance in hospitals having departments of obstetrics and gynecology. Systematic training in pathology, although desirable, is frequently not available in the prolonged education of the average obstetrician or gynecologist. Intelligent therapy of the female patient demands mastering the clinical pathological fundamentals and relationships. With these specific principles in mind, extreme wordiness and personal opinions were avoided. A straight forward tabulation of existing knowledge was attempted.

The first chapter is devoted to the technical handling of surgical specimens for histopathologic preparations. The histology of various types of epithelia and types of glands found in the female generative tract are appropriate introductory chapters. The next eight chapters deal with the specific problems of the pathology of the vulva, vagina, cervix, endometrium, myometrium, endometriosis, fallopian tube and ovary. Chapter eleven, the final chapter, summarizes the pathology of pregnancy in fifty one pages.

The photographs and photomicrographs are well selected and pertinent, and add to the clarity of the concisely presented text. The volume is beautifully bound and printed, with almost one illustration on each page.

The authors decided against the use of a bibliography although direct references to important works are made in the text when indicated. This may or may not be advantageous, but as previously mentioned it was the authors' purpose to write a book for students.

This book covers the breadth and scope of the field of obstetrical and gynecological pathology. Since there are relatively few treatises in the English language on this special phase of pathology, the book should be timely and well received. It will furnish a starting point for students and house officers requiring an introduction to the functional pathology of the female generative tract.

G. W. A.

Skin Grafting, new 2nd edition. By JAMES BARRETT BROWN and FRANK MCDOWELL. 339 pp. $7.50. *J. B. Lippincott Co., Philadelphia, Pa.*

These 300 pages greatly enlarge the scope of the first edition by these same authors. Whereas the original volume was devoted to burns, the new book covers almost the entire field of traumatic injuries producing skin loss.

The material is fresh, nicely illustrated, and unencumbered by excessive references and historical material. It presents a concise method of approach to the problems of wound care and skin replacement. It is a consolidation of the vast experience of these authors in both civilian and military surgery. It is all first hand experience.

For the medical student this volume offers the most easily readable introduction to plastic surgery now available. There are repeated illustrations of the limitations of plastic surgery—a phase of this surgical specialty that has been often neglected.

For the house officer or the general surgeon this book will be of great value in extending the use of truly modern methods in the treatment of large skin loss.

The chapters of the book which are devoted to the various regions of the body serve to point out the pitfalls and precautions that must be remembered.

The plastic surgeon is able to compare his results and techniques with those of the authors and to evolve a methodology that should greatly improve his total patient care. There are many details of a fundamental nature in this book that have previously escaped the general literature of plastic surgery.

The chapter on plastic surgery of World War II is of great interest. Attention is called to the importance of early grafting, of free split thick grafts when feasible, of composite grafting from the ear for nasal defects, and of the use of supraclavicular full thickness grafts for facial defects. Those of us who witnessed the work at Valley Forge Hospital are reminded of Dr. Brown's insistence that the plastic surgeon must assume patience, consideration, and optimism in dealing with many of these difficult, long term problems. This section, in a sense, is a tribute to the patients at Valley Forge and the courage they displayed.

M. T. E.

A Textbook of Surgery, 5th edition. Edited by FREDERICK CHRISTOPHER. 1550 pp. $13.00. *W. B. Saunders and Company, Philadelphia, Pa.*

This concise, practical treatise on surgery has, in its fifth edition, attained encyclopedic though not unwieldy proportions. In making the book an up-to-date cross-sectional presentation of the best in American surgery, the editor has collected contributions of 198 authors. These contributors, outstanding in their respective fields, are nearly all actively engaged in teaching surgery.

As in previous editions, the individual sections of the text comprise clearly authoritative presentations chiefly limited to the fundamental principles of clinical surgery. In this regard the book is of particular value to the student. Debatable and controversial issues over method of therapy are omitted; emphasis is placed upon etiology, pathology and diagnosis. Surgical treatment is carefully outlined and the principles of operative procedures are described. Technical aspects are in most instances not stressed. Illustrations and diagrams of the various lesions and of some operations have been improved in this edition and their number increased. The format is pleasing, on the whole, especially since the page text is broken into two columns as in the fourth edition.

Thirty entirely new sections have been added. Notable among these are chapters on infections and tumors of tendons; brain tumors and abscesses; tumors of the nose, sinuses and nasopharynx; gastric ulcer; diseases of the pancreas, and of the spleen; inguinal hernia; injuries of the kidney; and preoperative and postoperative care. In addition, nine sections have been extensively altered or revised by new authors. The revised chapter on anomalies of the small intestine and bile ducts by Dr. William E. Ladd is especially well presented.

In expanding its scope, this new edition of Dr. Christopher's text succeeds in encompassing the surgical specialties with worthy completeness. While its bibliographies are often necessarily sketchy, it is beautifully collected and adequately indexed. It remains a one-volume classic of the surgery of our time.

T. N. P. J.

BOOKS RECEIVED

Atlas of Human Sex Anatomy, 2nd edition. By ROBERT LATOU DICKINSON. 145 pp. $10.00. *The Williams and Wilkins Co. Baltimore, Md.*

Clinical Pathology: Application and Interpretation. By BENJAMIN B. WELLS. 397 pp. $6.00. *W. B. Saunders Co., Philadelphia, Pa.*

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